"HUNGRY BONE SYNDROME IN THYROTOXICOSIS AS A CAUSE OF POSTOPERATIVE HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY – A PROSPECTIVE STUDY"

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CERTIFICATE

This is to certify that the dissertation titled "**HUNGRY BONE SYNDROME IN THYROTOXICOSIS AS A CAUSE OF POSTOPERATIVE HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY – A PROSPECTIVE STUDY"** submitted by **Dr.K.POONGKODI** appearing for **M.Ch.** degree Branch - IX **ENDOCRINE SURGERY** examination in August 2014 is a bonafide record of work done by her under our guidance and supervision in partial fulfillment of requirement of the TamilNadu Dr. M.G.R Medical University, Chennai. I forward this to the TamilNadu Dr. M.G.R Medical University, Chennai.

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DECLARATION

I solemnly declare that this dissertation titled "**HUNGRY BONE SYNDROME IN THYROTOXICOSIS AS A CAUSE OF POSTOPERATIVE HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY – A PROSPECTIVE STUDY**" was prepared by me in the Department of Endocrine surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof.M.N.KAMALUDEEN M.S,** Professor & Head of the Department of Endocrine surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai and my ICMR guide Prof.M.Chandrasekaran MS., Former Professor and Head, Department of Endocrine surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the M.Ch degree Branch IX – Endocrine surgery examinations August 2014.

Place: Chennai

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CONTENTS

HUNGRY BONE SYNDROME IN THYROTOXICOSIS AS A CAUSE OF POSTOPERATIVE HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY- A PROSPECTIVE STUDY

BACKGROUND

Postoperative hypocalcemia, a well known complication of total thyroidectomy has a higher incidence in thyrotoxic patients than euthyroids. Though hypoparathyroidism is considered to be the important cause, other potential causes such as hungry bone syndrome (HBS) is not well established. Therefore we designed this prospective case control study to test the causal of hypothesis of hungry bone syndrome as a cause of postoperative hypocalcemia after total thyroidectomy among thyrotoxic patients.

MATERIALS AND METHODS

Forty clinically active hyperthyroid patients and 31 age and sex matched euthyoid patients were included in the study and control group respectively. Bone mineral density (BMD) at femur, lumbar vertebrae and forearm were measured initially at the time of diagnosis and six after total thyroidectomy in both groups. Baseline serum corrected calcium, phosphorus, magnesium, alkaline phosphatase and 25-OH VitaminD and serially thereafter in the postoperative period were measured in either group. The results were analysed with SPSS ver. 20 and p value <0.05 was considered significant.

RESULTS: The mean age of hyperthyroid patients (M: F= 19:21) and euthyroid controls (M: F = 8:23) were 36.48+/-9.84 and 33.9+/-9.012 respectively. The incidence of postoperative hypocalcemia was higher among hyperthyroid cases at 82.5% as compared to 22.5% amongst euthyroid controls (Odd's ratio=16.16, p<0.001). The incidence of HBS was 32.5% among thyrotoxic cases (Male: Female= 7:6) and constituted 39.5% of the cause for hypocalcemia. Transient hypoparathyroidism at71.4% constituted the major cause of hypocalcemia among euthyroid controls. Baseline BMD at femur, spine and forearm (the values of which were 0.8512+/-0.1647 g/cm^2, 0.9846+/-0.1676 g/cm^2 and 0.643+/-0.1133 g/cm^2) were significantly lower than euthyroid controls (which were 1.012+/-0128 g/cm^2, 1.129+/- 0.115 g/cm^2 and 0.751+/- 0.108 $g/cm^{2,}$ p<0.001). There was significant negative correlation between baseline femoral and lumbar BMD and serum alkaline phosphatase. Post treatment BMD revealed significant percent increment of 8.27% and 7.58% at femur and lumbar spine respectively.

CONCLUSION: Post-thyroidectomy hypocalcemia was higher in thyrotoxic patient and HBS contributed to 39.5% of the cause whereas transient hypoparathyroidism was the major determinant among euthyroid controls. Elevated serum alkaline phosphatase and low preoperative magnesium (especially in young females) were the predictive risk factors among thyrotoxic and euthyroid controls respectively.

INTRODUCTION

Postoperative hypocalcaemia is a common complication following thyroidectomy with reported incidence varying from 1.6 to as high as 83%[1-7]. Damage, devascularization or inadvertent removal of the parathyroid glands is the most important determinant, but other potential causes include “hungry bone syndrome” (HBS) due to postoperative reversal of thyrotoxic osteodystrophy[8], reactive hypoparathyroidism due to relative hypercalcaemia in thyrotoxic patients[9] and release of calcitonin during operative manipulation[10]. Hungry bone syndrome usually occurs as a complication after parathyroidectomy for hyperparathyroidism. But hungry bone syndrome occurring after thyroidectomy for thyrotoxicosis has not been established as the cause of hypocalcemia in prospective studies. Therefore, we designed this prospective case control study to determine the contribution of hungry bone syndrome as a cause of post-thyroidectomy hypocalcemia among thyrotoxic patients. We evaluated the longitudinal changes in bone mineral density and factors related to bone mineral ion homeostasis among thyrotoxic patients. We compared the same with age and sex matched euthyroid controls.

AIM OF THE STUDY

Primary objective:

To prospectively evaluate the incidence of hungry bone syndrome as a cause of post-thyroidectomy hypocalcemia among thyrotoxic patients.

Secondary objective:

- To evaluate the changes in the bone mineral density at all three sites, namely, femur, lumbar vertebrae and forearm before and after definitive surgical treatment
- To serially study the factors related to bone mineral ion homeostasis namely Serum calcium, phosphorus, magnesium, 25-hydroxy Vitamin D, intact Parathormone & Alkaline phosphatase and predict at risk patients likely to develop post operative hypocalcemia.

REVIEW OF LITERATURE

Thyroidectomy is the most common endocrine surgery performed worldwide. Theodor Kocher was awarded noble prize in 1909 for his pioneering work in thyroid surgery. He recognized the importance of anti- and aseptic handling, hemostasis, and precise operative technique which led to a reduction in mortality from high initial figures (50%) to less than 4.5%. Currently, the mortality rate of thyroidectomy approaches zero. However, morbidity remains a subject of concern as it leads to extended hospital stay. Postoperative hypocalcemia and vocal cord paralysis due to injury to the recurrent laryngeal nerve are the most common complications of total thyroidectomy.

Postoperative hypocalcemia is of particular concern because it manifests late usually in the 3rd or 4th postoperative day. This in turn requires prolonged patient hospitalization or readmission. Hypocalcaemia may be transient or permanent (persistent for more than 6 months after surgery). The reported incidence of transient hypocalcemia varies from 1.6 to 53.5%. Permanent hypoparathyroidism after total thyroidectomy is found in 1.5 to 4% of the patients.

The causes of hypocalcemia after Total thyroidectomy are multifactorial.

Damage, devascularization or inadvertent removal of the parathyroid glands are the major determinants of hypoparathyroidism. The presence of retrosternal extension, concomitant neck dissections, hyperthyroidism, thyroiditis, thyroid carcinoma, experience of the surgeon, prolonged operative time, and number of parathyroid glands left insitu also contribute to hypocalcemia.

FACTORS INFLUENCING HYPOPARATHYROIDISM

SURGICAL ANATOMY OF PARATHYROID:

Sound knowledge of anatomy together with meticulous tissue handling and safe surgical techniques help to preserve the vascularisation of the parathyroids.

Superior parathyroid develop from the dorsal aspect of fourth pharyngeal endodermal pouch and more constant in position. It is usually situated in the posterior aspect of the junction of upper and middle third of the lateral lobe of thyroid. It is dorsal to the recurrent laryngeal nerve.

Inferior parathyroid develops from the endoderm of the third pharyngeal pouch along with thymus. Due to the embryonic descent along with thymus, it is more inconstant in position. It is located near the inferior pole of the thyroid lobe or in the thyrothymic ligament and ventral to the recurrent laryngeal nerve.

ARTERIAL SUPPLY OF PARATHYROIDS:

The arterial blood supply to the parathyroid is single and terminal. Both the superior and inferior parathyroids receive its blood supply from glandular branches of inferior thyroid artery in 80% of the cases. They may also derive blood supply from the branches of superior thyroid artery, anastomotic branches between the two system or Neubaer artery, tracheoesophageal branches and arterial branches from the thyroid capsule. Capsular dissection with ligation of individual branches rather than ligation of the trunk of inferior thyroid artery preserves the blood supply to the parathyroids.

VENOUS DRAINAGE OF PARATHYROIDS:

Venous infarction of parathyroids may be relieved by superficial incision of its capsule.

NUMBER OF PARATHYROIDS PRESERVED:

All the four parathyroids should be identified and preserved. At least three parathyroids should be preserved to maintain calcium homeostasis. Some authors argue that single well vascularised parathyroid gland is sufficient to prevent permanent hypoparathyroidism. When the vascularity of the parathyroid is compromised or inadvertently removed, it is harvested and cut into fragments of less than 1 cu.mm and

autotransplanted into ipsilateral sternomastoid. This practice decreases the risk of permanent hypoparathyroidism to less than 1% [56, 57.]

IDENTIFICATION OF THE RECURRENT LARYNGEAL NERVE:

Extensive dissection required for the identification of the RLN may jeopardize the vascularity of the parathyroids.

OTHER CAUSES OF POSTOPERATIVE HYPOCALCEMIA

(a) HYPOMAGNESEMIA

Divalent magnesium ion is an orthosteric agonist at Calcium sensing receptor (CaSR) and has membrane stabilization and other physiological properties similar to Calcium ions. Both magnesium depletion and excess alters calcium homeostasis. Hypomagnesemia produces symptoms of neuromuscular irritability with or without concomitant hypocalcemia [15]. Hypomagnesemia causes functional hypoparathyroidism (i.e.) it decreases parathormone (PTH) secretion [17-19, 30] and increases target organ resistance to PTH as well as peripheral degradation of parathormone [20,21]. Magnesium deficiency is common in intensive care unit patients on parenteral nutrition, postoperative patients, chemotherapy, malnutrition etc[22-27]. Therefore, it is important to monitor serum magnesium in patients with persistent hypocalcemic symptoms

despite calcium therapy[28]. Magnesium replacement corrects hypocalcemia and hypokalemia.

(b) POSTOPERATIVE HEMODILUTION

The stress of surgery produces several metabolic alterations in the body. Acute volume loss during surgery triggers the pressor receptors in the carotid artery and the aortic arch and stretch receptors in the wall of the left atrium and the juxtaglomerular apparatus of the kidneys. These afferent stimuli cause the release of antidiuretic hormone (ADH) and activate the rennin-angiotensin system causing the release of aldosterone. Other afferent neurogenic stimuli related to the surgical trauma such as pain also causes activation of the above mechanisms. The end result of these mechanisms is fluid retention. In addition to the hormonal responses to a volume loss, there is a marked shift of fluid across the capillary beds into the blood stream. These phenomenon decreases the concentration of red blood cells (as measured by hematocrit) and cause a dilution in the serum protein concentration. This factor of hemodilution is attributed to the transient fall in total serum calcium levels in postoperative period after any major surgery and calcium levels return to normal preoperative value within 24-48 hours of surgery. Ionized serum calcium levels remains unaffected in this phenomenon.

(c) HYPOCALCEMIA IN GRAVES' DISEASE

Michie et al showed that an important cause for hypocalcemia after thyroidectomy for thyrotoxicosis was a rapid reversal of an osteodytrophy that existed before surgery. Excessive bleeding from increased vascularity in thyrotoxicosis may obscure surgical field and lead to parathyroid injury. In addition, autoimmune fibrosis compromising parathyroid vascularization may lead to hypoparathyroidism.

(d) EFFECT OF BLOOD TRANSFUSION:

Hypocalcemia may occur with rapid blood transfusion. The anticoagulants such as citrates present in the transfused blood may form complexes with calcium and lower total calcium levels.

(e) PREOPERATIVE INGESTION OF DRUGS

Anti-convulsants, chlorpromazine, diazepam, oral contraceptives, steroids and mithramycin have been known to cause hypocalcemia.

(f) HYPERPHOSPHATEMIA

Hyperphosphatemia can lower serum calcium. Hyperphosphatemia may occur due to hypoparathyroidism after total thyroidectomy or calcitriol supplementation. Hyperphosphatemia inhibits 1-alpha-hydroxylase activity in the kidney and decreases the conversion of 25-OH vitamin D to active 1, 25-Dihydroxy vitamin D. This in turn

aggravates hypocalcemia (due to reduced calcium absorption from the intestine).

EFFECT OF HYPERTHYROIDISM ON SKELETAL SYSTEM:

Thyrotoxicosis is defined as the clinical syndrome of hypermetabolism and hyperactivity that results when the serum concentrations of free thyroxine (T_4), free triiodothyronine (T_3), or both, are high. Hyperthyroidism is a subset of thyrotoxicosis characterized by increased synthesis and secretion of thyroid hormones.

The first systematic study of the clinical effects of thyrotoxicosis on the skeleton was published in 1972[1]. The skeleton is a metabolically active tissue in which mineralized bone is continuously remodeled by the coordinated recruitment of osteoclasts and osteoblasts that respectively cause bone resorption and bone formation. These processes are regulated by autocrine, paracrine, and endocrine pathways. Steroid hormones, particularly glucocorticoids, estrogens, androgens, and vitamin D, are particularly important regulators of bone metabolism.

In thyrotoxicosis, the processes of bone resorption, matrix deposition, and mineralization are accelerated and the activation frequency is increased. Osteoclast and osteoblast activities are both increased (albeit disproportionately), and the duration of the remodeling cycle is reduced by approximately 50%. The uncoupling of osteoclast-

osteoblast activation leads to an increase in the ratio of bone surface undergoing resorption to that undergoing formation. The net result is loss of bone, amounting to approximately 10% of mineralized bone per cycle in severe thyrotoxicosis. In keeping with increased activity of both osteoclasts and osteoblasts, serum and urinary biochemical markers of bone turnover are high in thyrotoxicosis. They include markers of both bone formation (serum alkaline phosphatase and osteocalcin) and bone resorption (urinary excretion of pyridinoline and deoxypyridinoline cross-links and hydroxyproline).

In addition to its direct effects on osteoclast-osteoblast cell function, thyrotoxicosis results in a negative calcium balance. Urinary calcium excretion is increased. Intestinal calcium absorption is decreased, and therefore fecal calcium excretion is increased. The increase in bone resorption raises serum calcium concentrations, sometimes enough to cause hypercalcemia. Any increase in serum calcium concentration inhibits parathyroid hormone secretion, thus accounting, at least in part, for the increase in urinary calcium excretion. Another consequence of decreased parathyroid hormone secretion is reduced renal conversion of 25-hydroxyvitamin D (calcidiol) to 1, 25 dihydroxyvitamin D (calcitriol). Reduced activation of vitamin D is exacerbated by increased metabolic clearance of vitamin D and its metabolites. Normal calcium homeostasis

and parathyroid hormone secretion are restored after treatment for thyrotoxicosis.

HUNGRY BONE SYNDROME (HBS)

HBS is characterized by rapid, profound and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesemia, due to an excessive bone remineralization. HBS is caused by the shift of calcium ion along with phosphorous and magnesium in to the hungry bones due to the sudden removal of stimulus for high bone turnover. The sudden removal of high circulating level of PTH following parathyroidectomy in hyperparathyroidism (and thyroidectomy in thyrotoxicosis) leads to sudden arrest of osteoclastic bone resorption in the phase of active bone turnover. This leads to enhanced bone remineralisation.

CLINICAL MANIFESTATION OF HBS

Hypocalcaemia causes neuromuscular irritability and manifests as acral and perioral parasthesia, positive Chvostek sign and Trousseau sign, carpopedal spam, laryngospasm, stridor, cardiac arrhythmia and congestive heart failure. In severe cases seizures, coma and death.

PREDISPOSING FACTORS FOR HBS

a) Advanced age [47]

b) High preoperative serum calcium

c) Two-fold elevation of serum alkaline phosphatase[47]

d) Preoperative low magnesium and albumin[47, 48]

e) Skeletal involvement(thyrotoxic osteodystrophy) [48-51]

f) Vitamin D depletion[48-51]

g) number of functional parathyroid left behind

BIOCHEMICAL CHANGES IN HBS

* Serum corrected serum calcium decreases to 8 mg/dl within 48-72 hours but further fall occurs after the fourth post-operative day in patients with HBS [47]

* Fall of Serum phosphate levels postoperatively

* Hypomagnesaemia

* 2- fold elevation of serum alkaline phosphatase

Sudden fall in intact parathormone to less than 1.7+/-0.4 pmol/l in PHPT. In contrast to PHPT, hypocalcemia of HBS in thyrotoxicosis is characterized by appropriate increases in parathormone.

MANAGEMENT OF HBS

Aim of the treatment is to

- Short-term - replenish the circulating calcium deficit.
- Long-term normalizing the bone turnover and remineralising skeleton.

TREATMENT OF HYPOCALCEMIA

Treatment of Acute hypocalcemia -

- 1 to 2 ampoules of Calcium gluconate (90 mg of elemental calcium per 10 mL ampoule) diluted in 50 to 100 mL of 5% dextrose is infused over 10 minutes
- Persistent hypercalcemia- infusion of calcium gluconate at a rate of 0.5-2.0 mg/kg/hour to maintain s.corrected calcium in low normal range
- Oral calcium supplementation is started simultaneously with vitamin D or its analogues (to aid calcium absorption from intestine)
- Correction of serum magnesium deficits- i.v magnesium sulphate at 48 mEq/ 24 hrs or oral Magnesium oxide200mg TDS for 3 days.

Adverse effects of intravenous calcium therapy

- Cardiac arrhythmias – rapid infusion>200 mg/100 mL of elemental calcium
- local extravasation into soft tissues (local irritation – Calcium chloride)
- Calcium phosphate crystal deposition- Ectopic calcification

TREATMENT OF CHRONIC HYPOCALCEMIA- PERMANENT HYPOPARATHYROIDISM

- Serum calcium is maintained at low normal range
    - Oral doses of 1 to 3 grams of elemental calcium in 3 to 4 divided doses- calcium carbonate (40% elemental calcium), calcium lactate (13%), calcium citrate (21%) and calcium gluconate (9%)
- Urinary calcium<4mg/kg/24hr (screen for nephrocalcinosis and hypercalciuria)
    - Thiazide diuretics may be used
    - Avoid furosemide
- If hypoparathyroidism- Serum 25 (OH) vitamin D levels maintained >20 ng/mL – vitamin D2or D3 or vitamin D metabolites supplementation
    - Calcitriol 0.25 mcg BD to 0.5 mcg QID
- Replacement with PTH for Hypoparathyroidism
    - Teriparatide- recombinant parathormone (1-34) 20mcg/day s.c

MATERIALS AND METHODS

STUDY DESIGN : Prospective case control study

PERIOD OF STUDY : November 2011 to February 2014

PLACE OF STUDY : Department of Endocrine Surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-600003.

SUBJECTS:

A total of 71 patients admitted in our department for surgery of benign thyroid diseases were included in the study and categorized selectively into two groups namely, study and control group. Institutional ethical committee's clearance and informed consent was obtained.

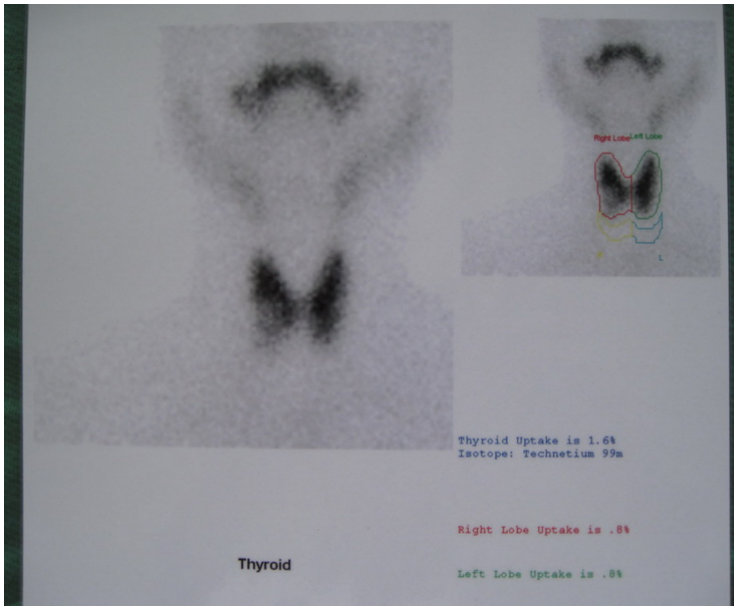
INCLUSION CRITERIA FOR STUDY/ TEST GROUP:

- 40 consecutive newly diagnosed clinically active hyperthyroid patients were recruited into the study/ test group
- Confirmed biochemically with elevated free triiodothyronine FT3, free tetraiodothyronine FT4 and suppressed Thyroid stimulating hormone TSH

- Confirmed by Technitium99m thyroid scintigraphy with increased radiotracer uptake and non- visualization of salivary glands
- Etiology of hyperthyroidism- 18 cases of Graves' disease and 22 cases of toxic multinodular goiter
- Patients likely to have surgery as the definitive modality of treatment-
    - Large volume goiter
    - Compressive symptoms of trachea, recurrent laryngeal nerve etc
    - logistic reasons requiring immediate definitive treatment,
    - cytology suspicious for malignancy,
    - associated ophthalmopathy,
    - patients planning for pregnancy within 4-6 months
    - Failure or non-compliance to medical treatment- antithyroid drugs.

Technetium scintigraphy of diffuse toxic goitre

Technetium scintigraphy – Multinodular goiter



EXCLUSION CRITERIA FOR STUDY GROUP:

- Patients with other causes of reduced BMD
    - long term steroids
    - immunosuppressive drugs
    - Chronic liver and kidney diseases
    - uncontrolled diabetes mellitus
    - smokers
    - alcoholics
- Parathyroid diseases

- Patients on Oral calcium and Vitamin D supplements, Thiazide diuretics

INCLUSION CRITERIA FOR CONTROL GROUP

36 cases of Age and sex matched euthyroid patients with benign multinodular goiter were included in the controls. Age variation up to 2 years was allowed. Patients were recruited at the same time as the test patients to avoid seasonal variation in 25 OH vitamin D levels. However, four male patients and 1 female patient were lost in the follow up and excluded from the study.

EXCLUSION CRITERIA

- Reoperative surgery
- Neck dissection
- Malignancy of thyroid
- Retrosternal extension

On admission, all subjects were subjected to thorough history taking and physical examination. Complete blood count, renal function test, liver function test, electrocardiogram, Ski gram of the chest, neck and thoracic inlet were done for anesthetic fitness. Specific investigations such as thyroid profile, thyroid autoantibodies, high frequency ultrasound neck, FNAC thyroid, ^{99m}Tc thyroid scintigraphy for confirming diagnosis.

Baseline BMD was evaluated at all three sites namely, femur, lumbar vertebrae and forearm using DEXA at the time of diagnosis of hyperthyroidism in the test group as well as euthyroid controls and 6 months after total thyroidectomy.

They were also analysed serially at the baseline, second and third post operative day and 6 months after surgery for the following biochemical indices,

1. Serum Corrected Calcium
2. Serum Phosphorus
3. Serum Magnesium
4. Serum 25-Hydroxy Vitamin D
5. Serum Parathormone
6. Serum Alkaline phosphatase (SAP)

Hyperthyroid patients received antithyroid drug Tab.carbimazole 10-60 mg/day in three divided doses and Tab.propranolol 40-160 mg/day in three divided doses and followed up with 4 to 6 weekly thyroid function test. On achieving clinical and biochemical euthyroids, surgery was done. Total thyroidectomy was the procedure of choice in either group or standardized technique was followed in all cases.

TECHNIQUE OF TOTAL THYROIDECTOMY

Under General Anesthesia, patient supine with neck hyperextension & reverse Trendelenburg's position, skin crease collar

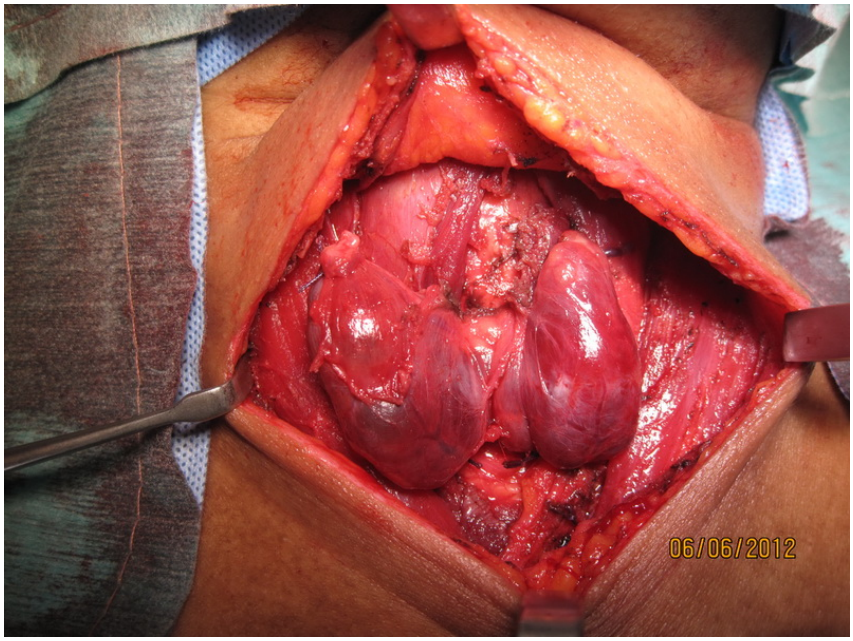
incision made. Subplatysmal flaps raised superiorly up to the upper border of thyroid cartilage and inferiorly up to the sterna notch. Deep cervical fascia opened midline. Sternohyoid retracted and sternothyroid divided as high as possible and thyroid gland exposed. Capsular dissection was carried out in the avascular plane.

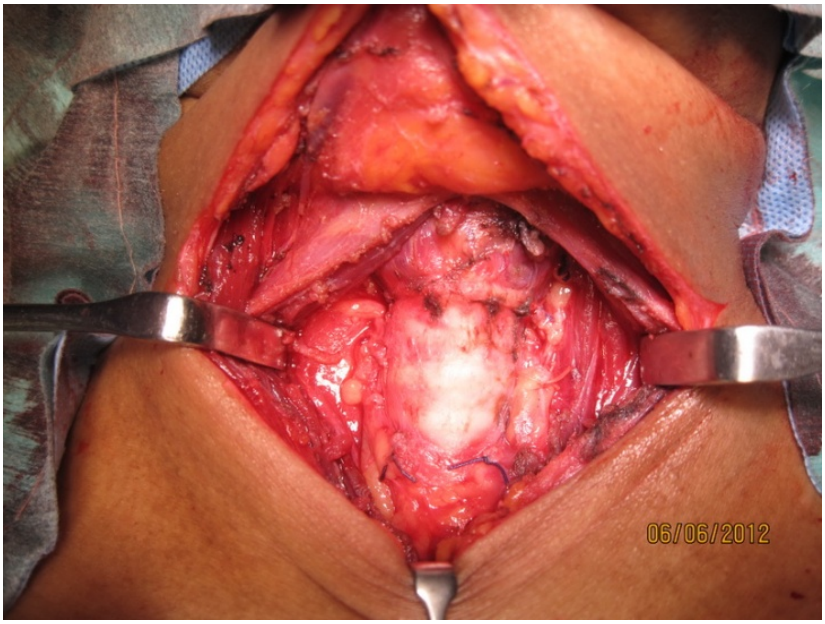
Sternothyroid laryngeal triangle was defined to identify external branch of superior laryngeal nerve (EBSLN). It is bounded medially by inferior constrictor and cricothyroid, laterally by superior pole of thyroid and anteriorly by sternothyroid muscle.

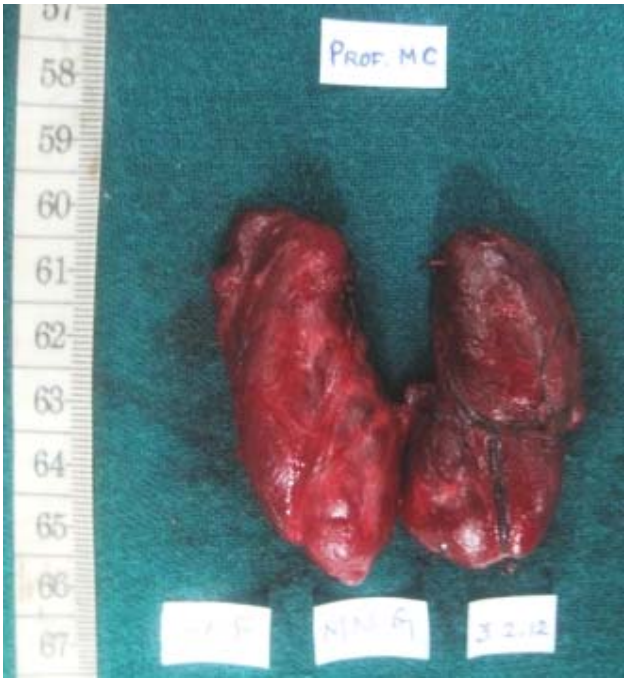
Superior Thyroid artery is ligated in continuity flushed with superior pole of thyroid away from EBSLN. Middle thyroid vein if present is ligated. Thyroid lobe is retracted medially. Recurrent laryngeal nerve (RLN) was identified in the trachea esophageal groove and laryngeal entry point noted on both sides.

The branches of the inferior thyroid artery are ligated separately very close to the gland. Efforts were taken to identify and preserve all four parathyroid glands. Superior parathyroid were identified on the posterior aspect of thyroid lobe within 1 cm from the intersection of RLN and inferior thyroid artery (ITA) dorsal to the RLN. Inferior parathyroid lie ventral to the RLN. If the parathyroid inadvertently was removed or vascularity seemed compromised, then autotransplantation was done in the homolateral sternocleidomastoid muscle. Closed suction drain was

placed as per surgeon's choice. Wound closed in layers. Surgical specimen sent for histopathological examination.






PROF. M C


Prof M.C
TOXIC MNG
Total Thyroidectomy
07/03/12

DENSITOMETRY METHODS:

Bone mineral density was measured by Dual energy X- ray Absorptiometry using the machine Lunar iDXA encore 2007 version11.30.062 GE Co., Madison, WI 53717-1915. Femoral BMD was measured at Femur neck, trochanteric and intertrochanteric region bilaterally. Lumbar BMD was measured in lumbar vertebrae L1 to L4. BMD forearm measured in long bones of forearm. The in- vivo precision for DPA were 1.7%, 1.6% and 1.8% at femoral, lumbar and forearm BMD. BMD was expressed in g/cm^2 , T- score (units of standard deviation from young healthy adult reference population) and Z- score (units of standard deviation from an age-, sex-, height-, and weight-adjusted mean). Bone involvement was analysed as per World Health Organisation criteria for osteoporosis.

Normal: T-score at or above -1 SD

Osteopenia: T-score between -1 & -2.5 SD

Osteoporosis: T-score at or below -2.5 SD

LABORATORY METHODS

Overnight fasting venous sample were collected from all patients at 700 to 800 hrs in calcium free test tubes and analysed for the following parameters. Free Triiodothyronine (2.0 – 4.4 pg/ml), Free Thyroxine

(0.79 -2.2 ng/dl) and Thyroid stimulating hormone (0.3-5.5 mIU/ml) are performed using ultrasensitive CLIA i.e. Chemiluminescent immunometric assay. Serum calcium was analysed by Arsenazo III method using Beckman Coulter pvt ltd in Synchron CX9. The coefficient of variation was 1.9% from a mean of 9.25 mg/dl. The corrected calcium (mg/dl) level was calculated by the formula (calcium concentration [mg/ dl] + 4-albumin [g/dl]) X0.8. Serum alkaline phosphatase (40-115 IU/L) was analysed by PNPP (p-nitrophenyl phosphate) and had a coefficient of variation of 5.8% from mean 107.0 IU. Serum phosphorus (2.5 -4.5 mg/dl) by Phosphomolybdate method using Beckman Coulter pvt ltd in Synchron CX9. Serum magnesium(1.7-3 mg/dl) was analysed by Calmagite method using Griner private ltd. in photometer 5010. Serum intact parathormone was measured by two site Chemiluminescent immunometric assay using Siemens pvt. Ltd with reference range (12 - 65pg/ml).Serum 25-OH vitamin D3 was measured by Chemiluminescent immunometric assay using Siemens pvt. Ltd ADVIA centaur with 5.4% coefficient of variation from mean 24.9 ng/ml with reference range as Deficiency< 12, insufficiency12-30, sufficiency>30 and Toxic >100 ng/ml.

Hypocalcaemia was defined as mild if serum corrected Ca^{2+} 7.8 to 8.3 mg/dl (i.e)1.96 –2.09 mmol/L and Severe if corrected Ca^{2+} < 7.8

mg/dl (<1.95 mmol/L); the normal range for Ca^{2+} was 8.4 to 10.2 mg/dl (2.10 to 2.55 mmol/L). Mild hypomagnesemia was defined as serum Mg^{2+} <1.7 mg/dl and severe hypomagnesemia if serum Mg^{2+}< 1.4 mg/dl; normal range was 1.7 – 3.5 mg/dl

Permanent hypoparathyroidism was defined by the requirement for oral calcium or vitamin D supplementation after 6 months from the time of thyroidectomy to maintain a eucalcemic state [11,12].

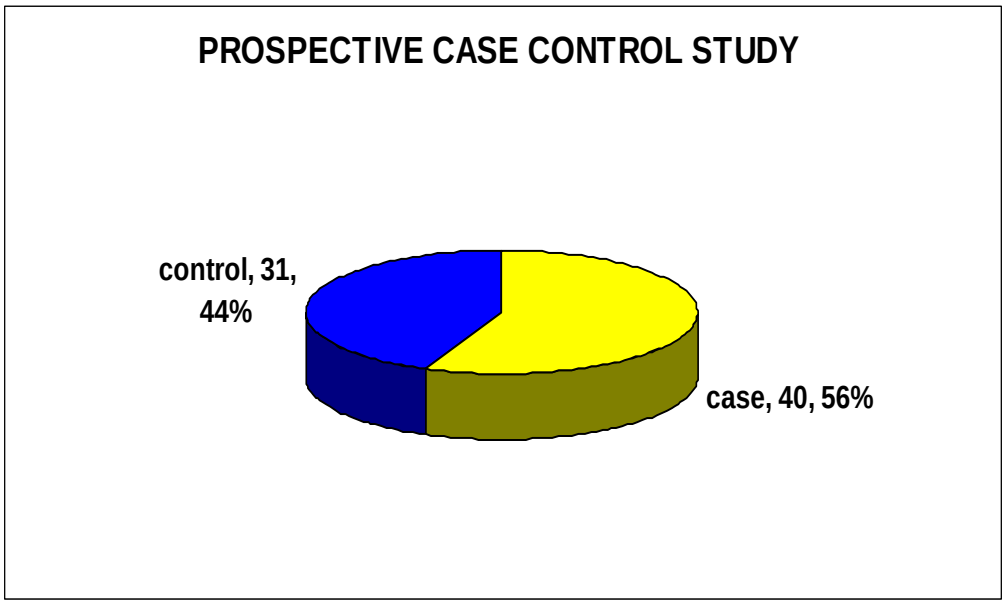
Symptoms of "hypocalcemia" were defined as acral or perioral paresthesia, carpopedal spasm, seizures, laryngeal stridor, or cardiac arrhythmias. Patients had Trousseau and Chvostek signs recorded after surgery. Severe hypocalcemia was treated with infusion of calcium gluconate at 1.5-2 mg/kg/hr and simultaneously with oral calcium carbonate (up to 3g/day elemental calcium) and calcitriol(up to 2 mcg/d). IV magnesium sulphate 2g/d and oral magnesium oxide 200mg TDS for 3 days may be required in hypomagnesemic patients. These patients were followed more frequently.

STATISTICAL ANALYSIS

Data were expressed as mean+/- standard deviation. Statistical analysis was performed with IBM SPSS statistics version 20.0. by two tailed paired student t- test, two tailed unpaired student t- test, Chi –

square test and analysis of variance ANOVA where appropriate. P value <0.05 was considered significant.

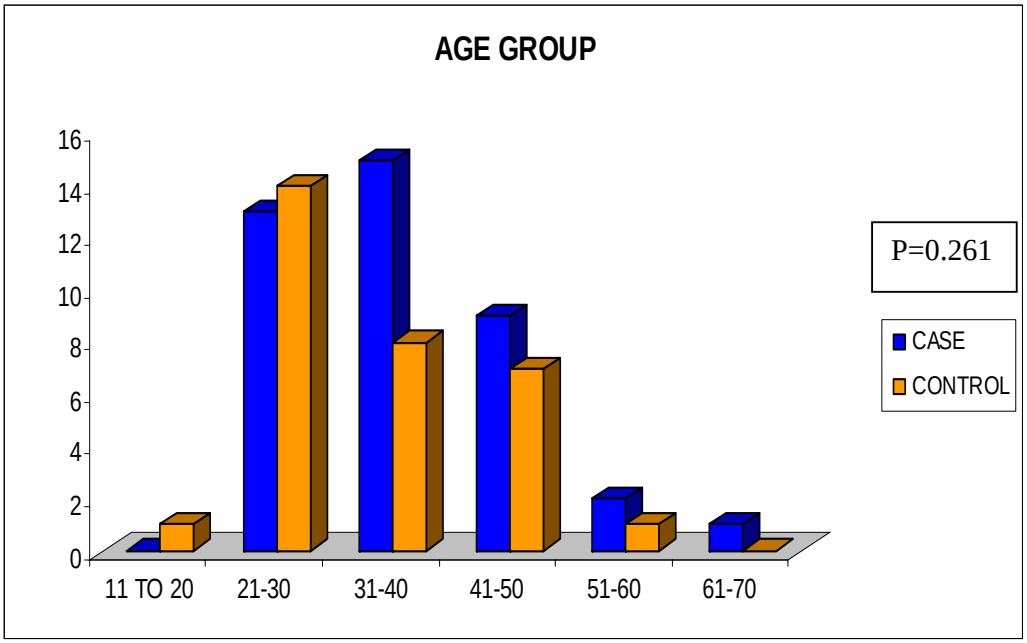
RESULTS



A total of 71 patients were included in the series. Study group consisted of 40 clinically active hyperthyroid cases and control group consisted of 31 euthyroid patients. Initially 36 patients were recruited in the control group but 34 men and I woman were lost in the follow up and excluded from the study.

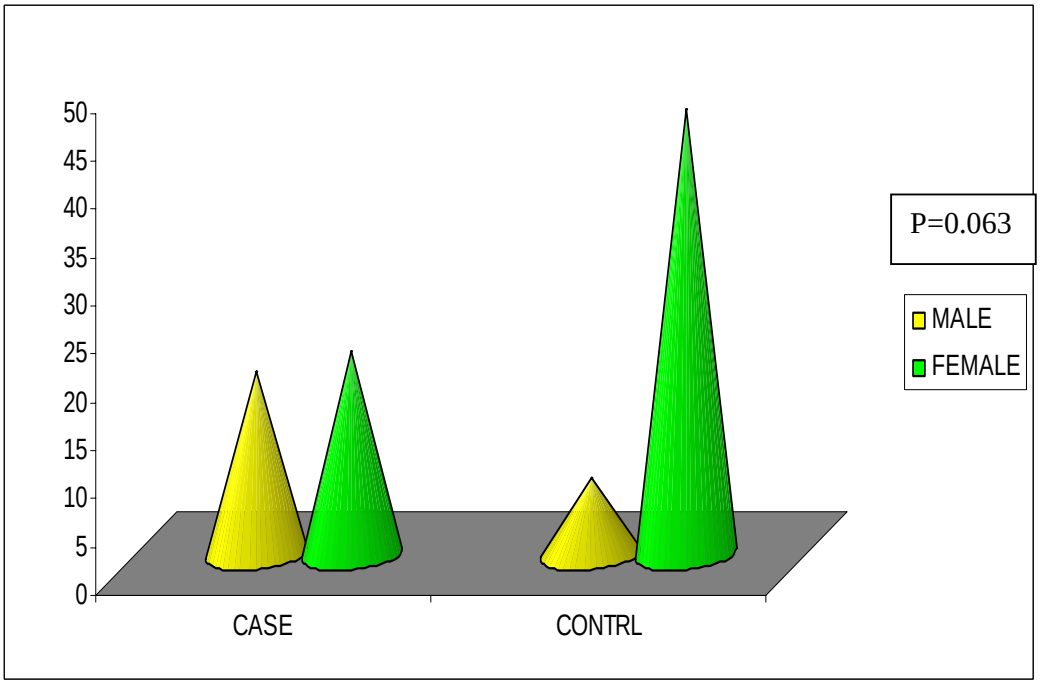
AGE DISTRIBUTION:

Most of the patients in either group were in the third and fourth decade of life with mean age of 36.48+/-9.84 and 33.9+/-9.012 in the study and control group respectively. Statistically there was no difference between the two groups with regard to age distribution (P= 0.261).



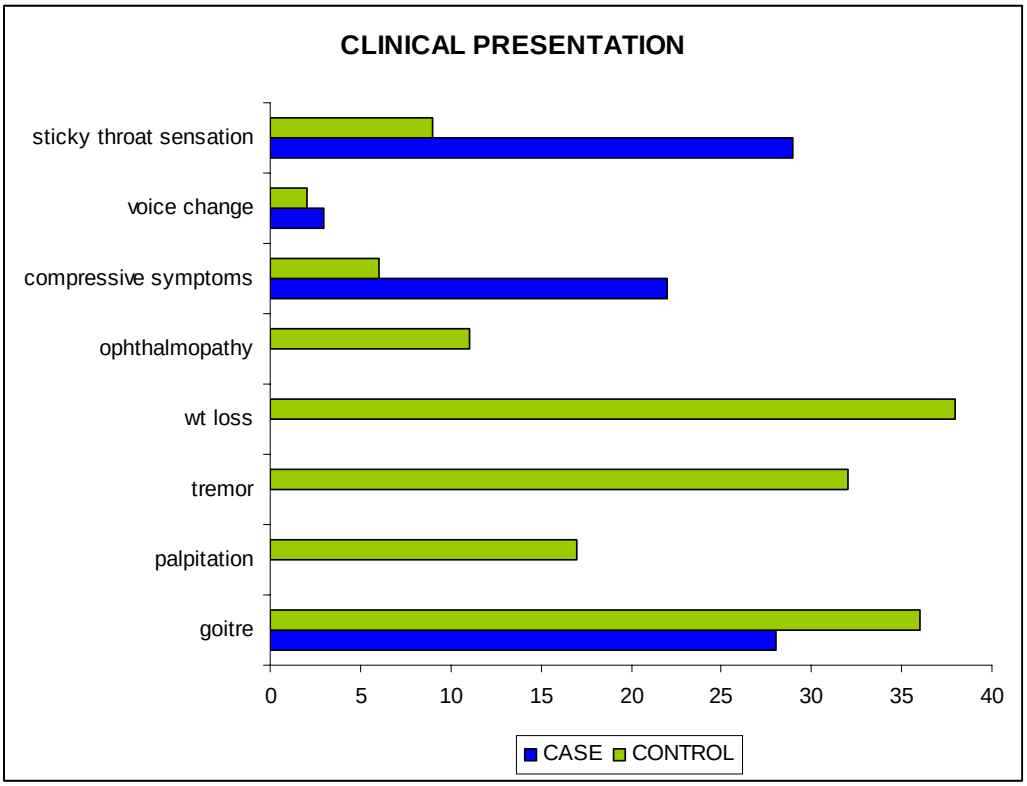
GENDER DISTRIBUTION:

Of the 40 hyperthyroid patients, there were 19 men and 21 women and among euthyroid controls, there were 8 men and 23 women. P=0.063.



CLINICAL PRESENTATION

Swelling in the front of neck in the region of thyroid was the most common presentation. However weight loss despite increased appetite was the next common presentation in study group. The mean weight among hyperthyroid was(47.2+/-8.6Kg) significantly lower than euthyroid controls(52.4+/-5.2 Kg).



Sticky throat sensation with compressive symptoms were the next common presentation among euthyroid controls.

Clinical and biochemical indices analysed between the two groups are given in the following Table.

S.No	PARAMETERS	CASE	CONTROL	P value
1.	Age in years	36.48+/-9.84	33.9+/-9.01	0.261
2.	Male: Female	19:21	8:23	0.063
3.	Weight in kg	47.2+/-8.6	52.4+/-5.2	<0.05
4.	Duration of disease in months	7.5+/-5.9	7.26+/-3.19	0.837
5.	Duration of antithyroid drugs in months	3.25+/-1.15	-	
6.	FT3 pg/ml	16.66+/-7.23	2.14+/-0.98	0.001
7.	FT4ng/dl	5.22+/-2.38	1.12+/-0.78	0.022
8.	TSHmIU/ml	0.011+/-0.018	2.84+/-1.15	0.043
9.	Anti Thyroperoxidase antibody	607.46+/-365.015	4.25+/-2.225	0.001
10.	Anti Thyroglobulin antibody	266.5+/-400.4	3.54+/-11.25	0.013

Thus, in the study group, free hormones were elevated and TSH suppressed. In addition the thyroid autoantibodies, namely Antithyroglobulin antibody and Anti-Thyroperoxidase antibody were elevated.

HISTOPATHOLOGY	CASE		CONTROL	
	Hyperplastic goitre	14	Nodular colloid goiter	14
	Toxic nodular goitre	18	colloid cystic goiter	4
	Hashimoto's thyroiditis	8	Follicular adenoma	6
			Adenomatous goiter	2
			Lymphocytic thyroiditis	5
TOTAL		**40**		**31**

MAJOR COMPLICATION	CASE	CONTROL
Transient hypocalcemia	32	7
Permanent Hypocalcemia	1	-
Temporary recurrent laryngeal nerve palsy	3	1
Permanent recurrent laryngeal nerve palsy	1	-

The biochemical indices related to bone mineral ion homeostasis which were measured serially are tabulated & compared between the study group and controls.

PARAMETERS	CASE	CONTROL	P VALUE	
PRETREATMENT				
S.CORRECTED CALCIUM mg/dl	9.13+/-0.66	9.45+/-0.73	0.055	NS
S.PHOSPHOROUS mg/dl	4.12+/-0.76	3.99+/-0.85	0.054	NS
S.MAGNESIUM mg/dl	1.78+/-0.67	2.18+/-0.45	0.004	S
S. INTACT PARATHORMONE pg/ml	50.56+/-35.61	42.66+/-16.73	0.218	NS
S.ALKALINE PHOSPHATASE IU/L	143.18+/-72.0	71.97+/-23.07	<0.001	S
S.25OH VITAMIND ng/ml	24.27+/-10.61	26.12+/-14.63	0.555	NS

From the above table, we observed that serum magnesium was significantly in the low normal range among hyperthyroid patients compared to euthyroid controls in the pretreatment phase. Serum alkaline phosphatase was two-fold higher than euthyroid controls.

The preoperative corrected serum calcium levels were in the normocalcemic range with mean value 9.13+/-0.66 among thyrotoxic patient in contrast to hypercalcemia reported in western literature. We

also observed that the 25-OH vitamin D were in the insufficient range in both groups and preoperative parathormone was high normal. The prevalence of hypovitaminosis D in our population leading to secondary hyperparathyroidism could be the probable reason.

PARAMETERS	CASE	CONTROL	P VALUE	
POSTOPERATIVE PHASE				
S.CORRECTED CALCIUM mg/dl	7.715+/-0.81	8.961+/-0.771	<0.001	S
S.PHOSPHOROUS mg/dl	4.16+/-1.20	4.23+/-0.76	0.792	NS
S.MAGNESIUM mg/dl	1.95+/-0.79	1.95+/-0.46	0.974	NS
S. INTACT PARATHORMONE pg/ml	29.67+/-21.97	18.89+/-12.73	0.012	S
S.ALKALINE PHOSPHATASE IU/L	120+/-51.99	65.68+/-20.34	<0.001	S

POSTOPERATIVE PHASE

Marked hypocalcemia was observed in the study group with a mean of 7.715 +/- 0.81 mg/dl in the postoperative phase. The magnitude of severity of hypocalcemia was also high as compared to the controls. However, intact parathormone was in the normal range among hyperthyroid cases. But it was significantly reduced in the control group.

Serum alkaline phosphatase showed two fold rise in the postoperative period in the study group.

FOLLOW UP				
PARAMETER	**CASE**	**CONTROL**	**P VALUE**	
S.CORRECTED CALCIUM mg/dl	8.88+/-0.69	8.58+/-1.72	0.927	NS
S.PHOSPHOROUS mg/dl	3.80+/-0.67	3.94+/-0.73	0.44	NS
S.MAGNESIUM mg/dl	2.21+/-0.34	2.26+/-0.32	0.533	NS
S.INTACT PARATHORMONE pg/ml	60.17+/-38.44	40.28+/-16.07	0.006	S
S.ALKALINE PHOSPHATASE IU/L	102.52+/-8.26	67.78+/-13.68	<0.001	S

Serum calcium returned to normocalcemic range 6 months after surgery in the hyperthyroid group. Intact parathormone climbed up to high normal range among throtoxic cases. Though there was a fall in serum alkaline phosphatase in the follow up, it still remained higher than euthyroid controls.

COMPARISON WITHIN THE GROUP

WITHIN THE STUDY GROUP

We observed a very significant fall in the level of serum calcium in the postoperative period. Though there was a drop in the parathormone postoperatively it was still in the normal range. Serum alkaline phosphatase remained two – fold higher than normal range.

ST UDY GROUP PREOPERATIVE VS POSTOPERATIVE

PARAMETER	PREOPERATIVE	POSTOPERATIVE	P VALUE
S.CORRECTED CALCIUM mg/dl	9.13+/-0.66	7.715+/-0.81	<0.001
S.PHOSPHOROUS mg/dl	4.12+/-0.76	4.16+/-1.20	0.829
S.MAGNESIUM mg/dl	1.78+/-0.67	1.935+/-0.79	0.319
S. INTACT PARATHORMONE pg/ml	50.56+/-35.61	29.67+/-21.97	0.005
S.ALKALINE PHOSPHATASE IU/L	143.18+/-72.0	120+/-51.99	0.011

STUDY GROUP- POSTOPERATIVE VS FOLLOW UP

PARAMETER	POSTOPERATIVE	FOLLOW UP	P VALUE
S.CORRECTED CALCIUM mg/dl	7.715+/-0.81	8.88+/-0.69	<0.001
S.PHOSPHOROUS mg/dl	4.16+/-1.20	3.80+/-0.67	0.035
S.MAGNESIUM mg/dl	1.935+/-0.79	2.21+/-0.31	0.020
S. INTACT PARATHORMONE pg/ml	29.67+/-21.97	60.17+/-38.44	<0.001
S.ALKALINE PHOSPHATASE IU/L	120+/-51.99	102.52+/-8.26	0.041

Serum calcium restored to normocalcemic range with concomitant increase in serum parathormone. Serum magnesium and phosphorus also returned to normal range. Though serum alkaline phosphatase showed a significant drop, it still remained elevated especially in those with osteoporosis or osteopenia. One case of permanent hypoparathyroidism occurred in the study group.

COMPARISON WITHIN THE CONTROL GROUP

We documented a significant fall in the level of corrected serum calcium and magnesium along with a rise in the level of phosphorus postoperatively in the euthyoid controls. Intact parathormone showed a significant drop to low normal values.

PARAMETER	PREOPERATIVE	POSTOPERATIVE	P VALUE
S.CORRECTED CALCIUM mg/dl	9.45+/-0.73	8.961+/-0.771	0.005
S.PHOSPHOROUS mg/dl	3.99+/-0.85	4.23+/-0.76	0.08
S.MAGNESIUM mg/dl	2.18+/-0.45	1.95+/-0.46	0.039
S. INTACT PARATHORMONE pg/ml	42.66+/-16.73	18.89+/-12.73	<0.001
S.ALKALINE PHOSPHATASE IU/L	71.97+/-23.07	65.68+/-20.34	0.021

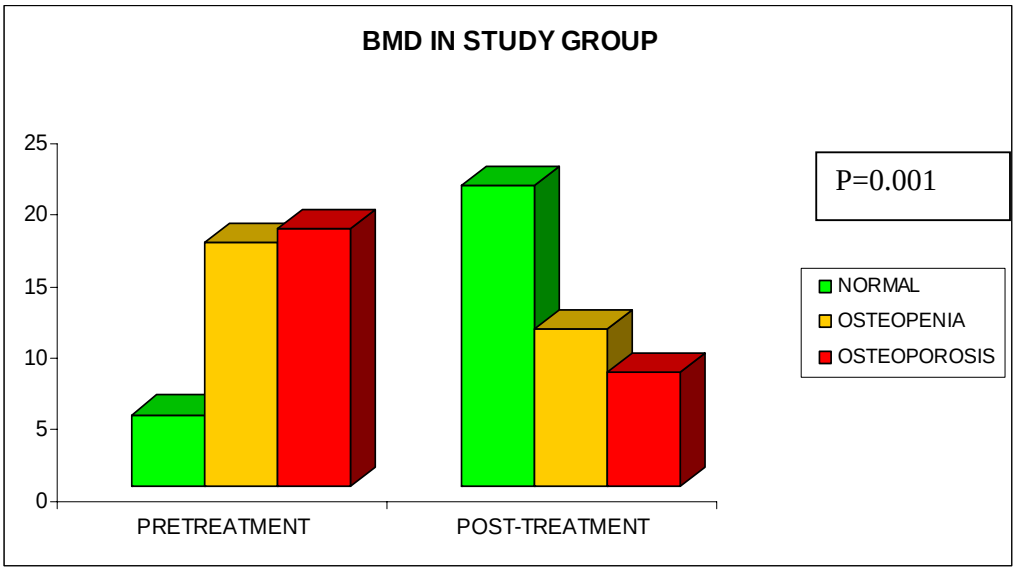
In the follow up surveillance, we documented a significant increase in the intact parathormone with normalization of calcium and phosphorus. Serum magnesium also improved significantly. All patients became asymptomatic.

CONTROL GROUP - POSTOPERATIVE VS FOLLOW UP

PARAMETER	POSTOPERATIVE	FOLLOW UP	P VALUE
S.CORRECTED CALCIUM mg/dl	8.961+/-0.771	8.58+/-1.72	0.313
S.PHOSPHOROUS mg/dl	4.23+/-0.76	3.94+/-0.73	0.043
S.MAGNESIUM mg/dl	1.95+/-0.46	2.26+/-0.32	0.001
S. INTACT PARATHORMONE pg/ml	18.89+/-12.73	40.28+/-16.07	<0.001
S.ALKALINE PHOSPHATASE IU/L	65.68+/-20.34	67.78+/-13.68	0.903

There was no significant change in the levels of serum alkaline phosphatase among the euthyroid controls.

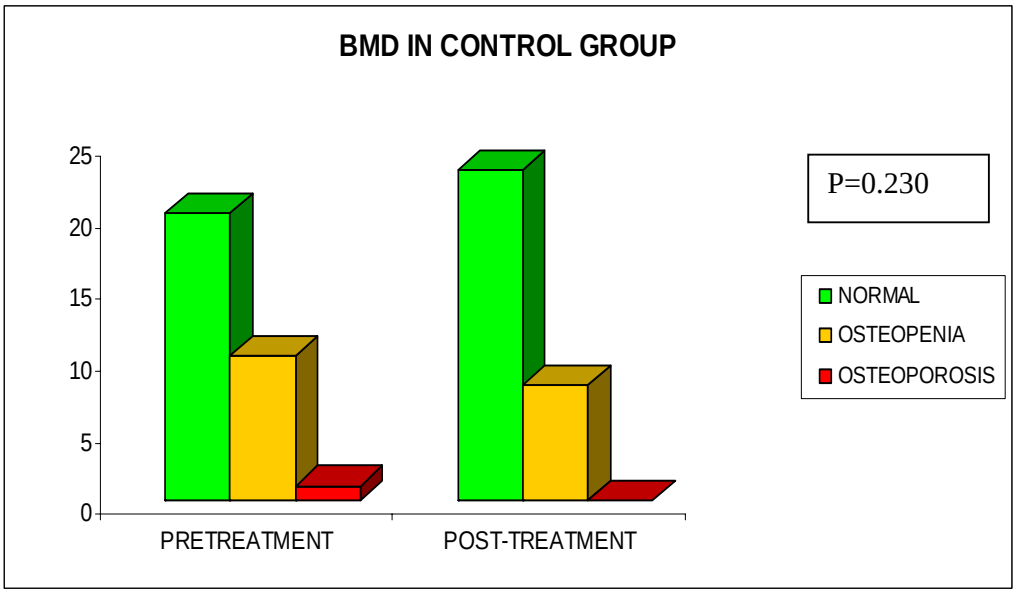
EVALUATION OF BONE MINERAL DENSITY IN STUDY VS CONTROL



BMD IN STUDY GROUP				
DEXA SCAN	**PRETREATMENT**		**POST-TREATMENT**	
NORMAL	5	12.5%	21	52.5%
OSTEOPENIA	17	42.5%	11	27.5%
OSTEOPOROSIS	18	45%	8	20%
TOTAL	40	100%	40	100%

Pretreatment DEXA revealed bone involvement in 87.5% of the hyperthyroid cases initially at the time of diagnosis of hyperthyroidism. We documented osteopenia in 42.5% and osteoporosis in 45% of the

hyperthyroid cases. Post-treatment DEXA scan taken 6 months after surgery showed significant improvement in the BMD ($p<0.001$) and normalized in 52.5% of the cases.

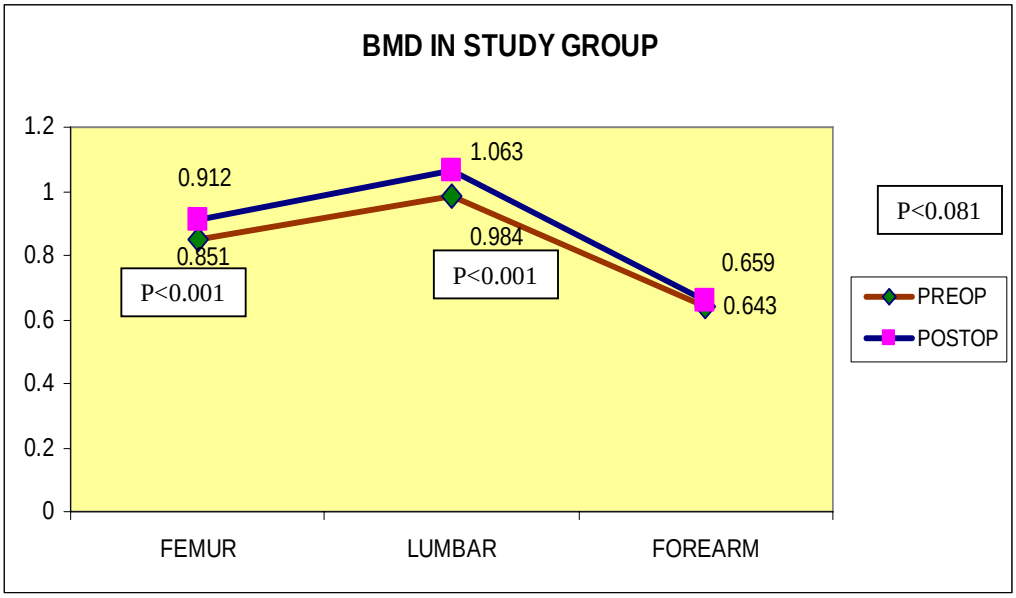


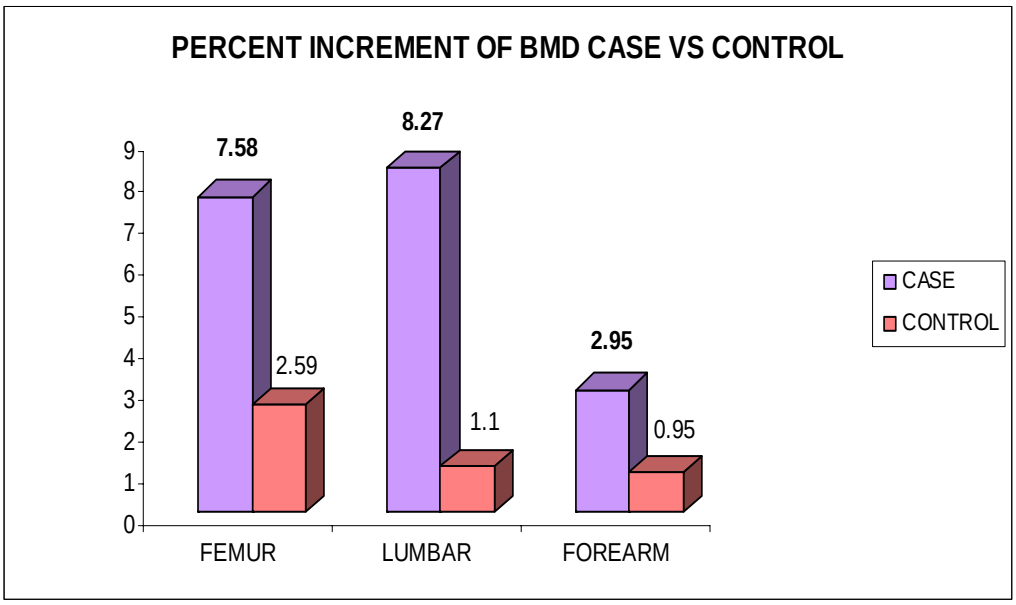
BMD IN CONTROL GROUP				
DEXA	**PRETREATMENT**		**POST-TREATMENT**	
NORMAL	20	64.51%	23	74.19%
OSTEOPENIA	10	32.25%	8	25.80%
OSTEOPOROSIS	1	3.22%	0	0
TOTAL	31	100%	31	100%

On the other hand, pretreatment DEXA was normal in majority of the euthyroid controls and not much change after surgery.

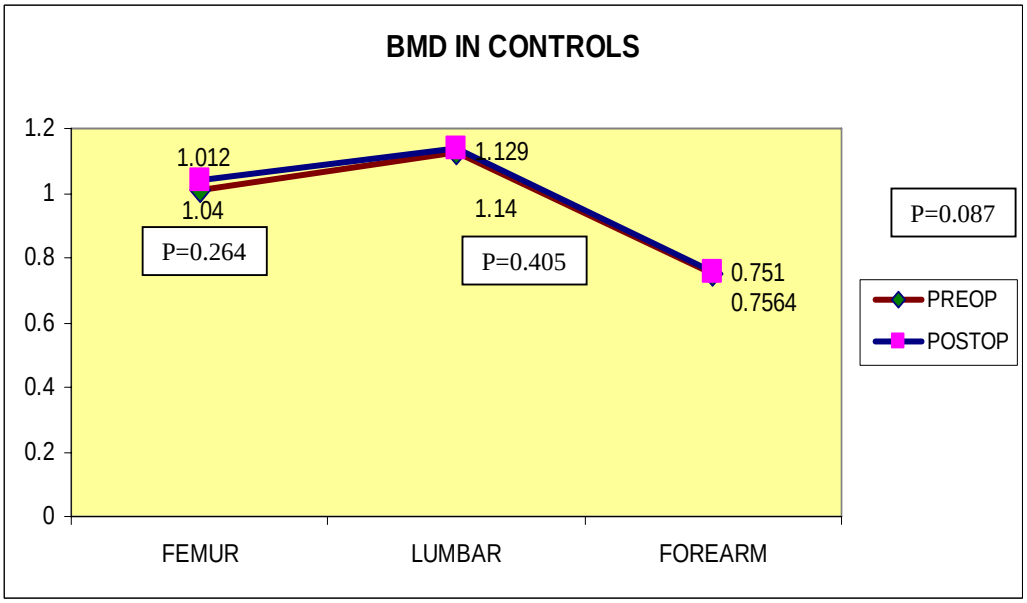
Baseline Femoral, lumbar and forearm BMD were 0.8512+/- 0.1647 g/cm^2, 0.9846+/-0.1676 g/cm^2 and 0.643+/-0.1133 g/cm^2 respectively among hyperthyroid cases and were 1.012+/-0128 g/cm^2, 1.129+/- 0.115 g/cm^2 and 0.751+/- 0.108 g/cm^2 respectively among euthyroid controls. Thus, BMD at all three sites were significantly lower among hyperthyroid s than euthyroid controls (p value<0.001).

After definitive surgical management, the bone mass improved predominantly in the femur and lumbar vertebrae (p value < 0.001) among hyperthyroid cases. Although the bone mineral density did increase at forearm, the mean increment was not statistically significant (p value = 0.081).

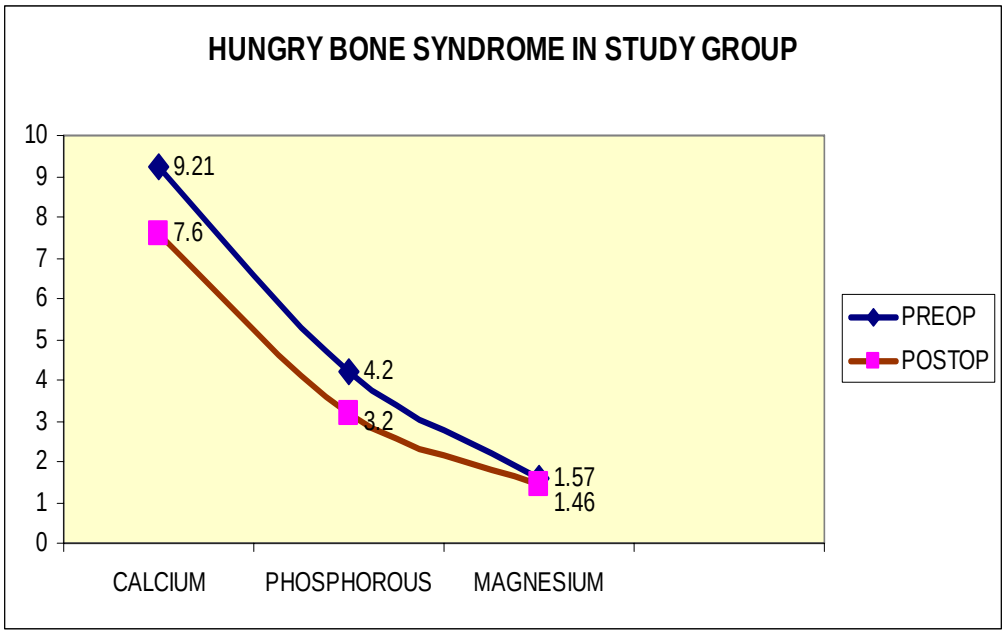


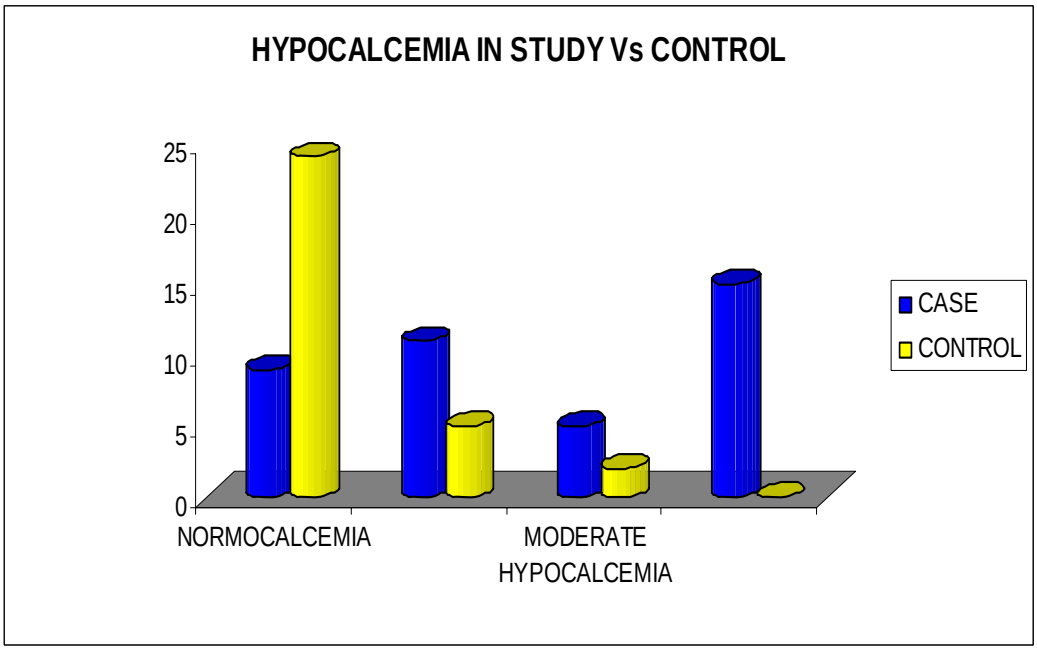


The percent increment in the bone mass was highest in lumbar vertebrae at 8.27%, followed by femur at 7.58% and least in the forearm (2.95%).



There was not significant change in the BMD of the controls before and after treatment.

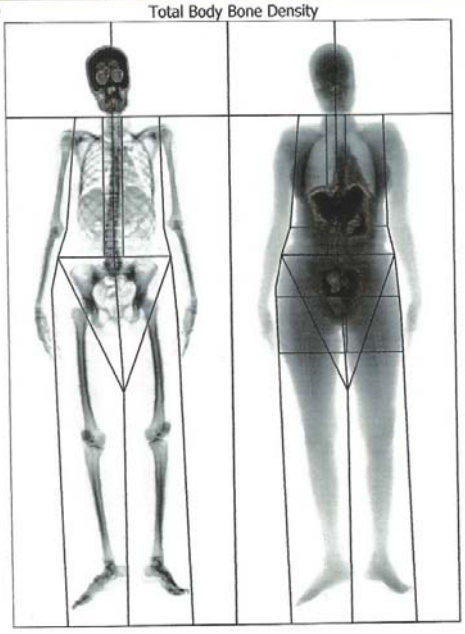

HUNGRY BONE SYNDROME IN STUDY GROUP
10
9
8
7
6
5
4
3
2
1
0
9.21
7.6
4.2
3.2
1.57
1.46
CALCIUM
PHOSPHOROUS
MAGNESIUM
PREOP
POSTOP


HYPOCALCEMIA IN STUDY Vs CONTROL
25
20
15
10
5
0
NORMOCALCEMIA
MODERATE HYPOCALCEMIA
CASE
CONTROL

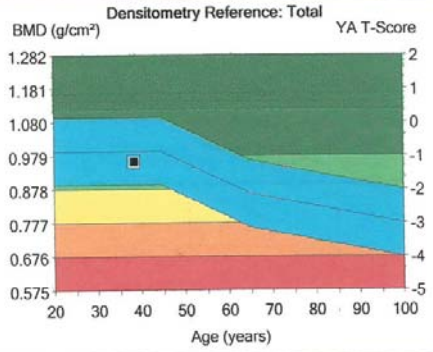
PRE & POST TREATMENT TOTAL BODY BMD

Patient:	MRS.ABIRAMI.S,	**Patient ID:**	101231085
Birth Date:	01/01/1974 38.4 years	**Referring Physician:**	PROF CHANDRASEKARAN M MS
Height / Weight:	146.0 cm 44.5 kg	**Measured:**	16/06/2012 11:27:45 AM (11.30)
Sex / Ethnic:	Female White	**Analyzed:**	16/06/2012 11:32:19 AM (11.30)

Total Body Bone Density

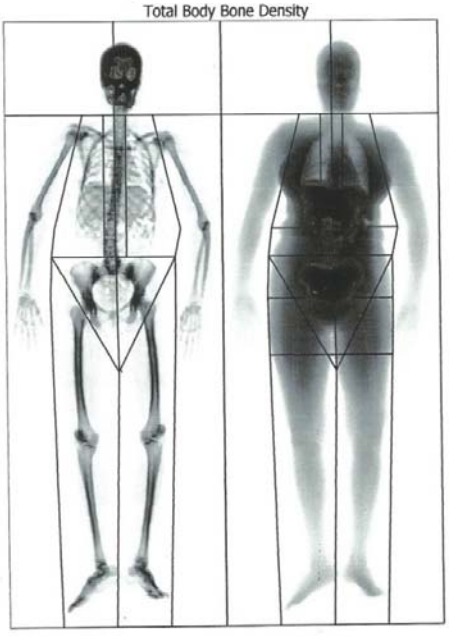


Densitometry Reference: Total

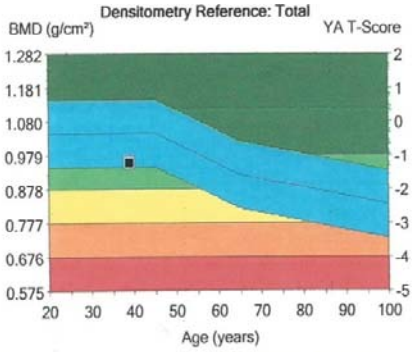


Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
Head	1.864	-	-
Arms	0.751	-	-
Legs	0.960	-	-
Trunk	0.766	-	-
Ribs	0.670	-	-
Pelvis	0.790	-	-
Spine	0.841	-	-
Total	0.960	-1.2	-0.3

Total Body Bone Density

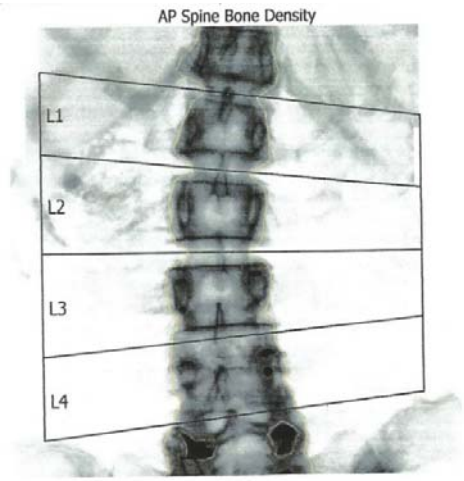


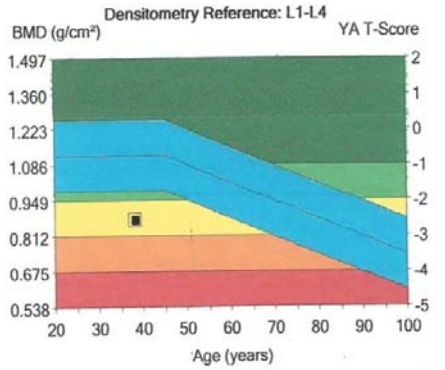
Densitometry Reference: Total



Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
Head	1.839	-	-
Arms	0.632	-	-
Legs	1.010	-	-
Trunk	0.832	-	-
Ribs	0.727	-	-
Pelvis	0.871	-	-
Spine	0.905	-	-
Total	0.956	-1.2	-0.9

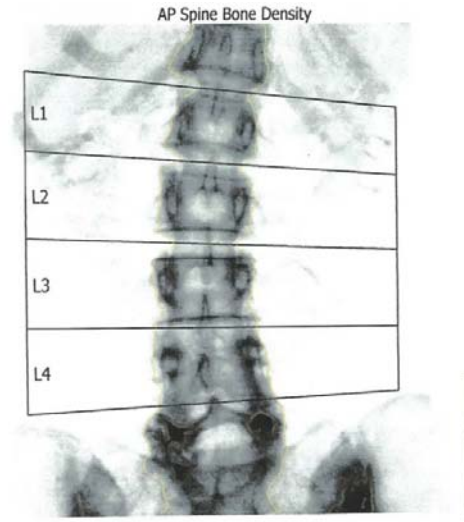
PRE TREATMENT LUMBAR VERTEBRAE BMD -OSTEOPOROSIS

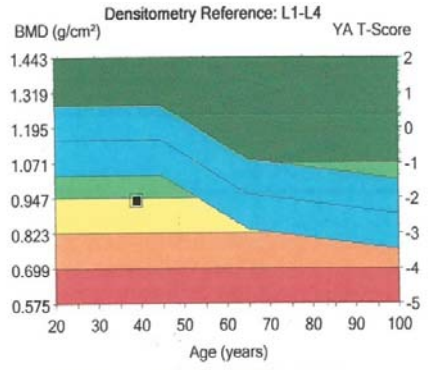




Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
L1	0.845	-2.0	-1.3
L2	0.815	-2.9	-2.3
L3	0.893	-2.7	-2.1
L4	0.915	-2.1	-1.6
L1-L4	0.871	-2.6	-1.9

POST TREATMENT LUMBAR VERTEBRAE BMD –OSTEOPENIA





Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
L1	0.887	-2.1	-1.8
L2	0.881	-2.7	-2.5
L3	0.976	-1.9	-1.7
L4	0.985	-1.8	-1.6
L1-L4	0.938	-2.1	-1.8

PRETREATMENT & POSTTREATMENT – FEMUR

DualFemur Bone Density

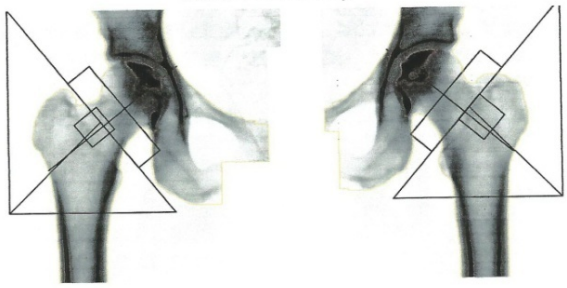
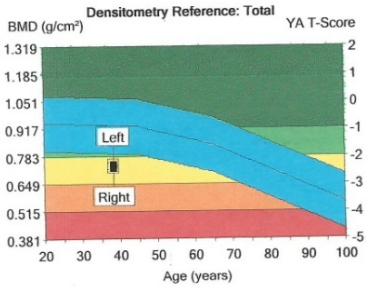
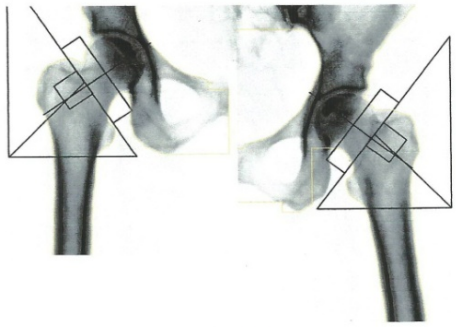


Image not for diagnosis



Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score
Neck			
Left	0.736	-2.2	-1.3
Right	0.787	-1.8	-0.9
Mean	0.762	-2.0	-1.1
Difference	0.051	0.4	0.4
Total			
Left	0.742	-2.3	-1.4
Right	0.725	-2.4	-1.5
Mean	0.733	-2.4	-1.5
Difference	0.017	0.1	0.1

DualFemur Bone Density



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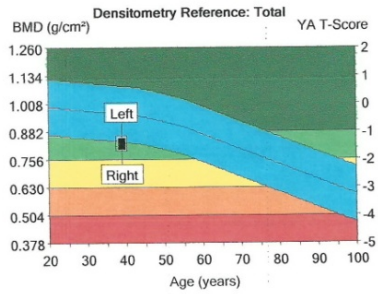
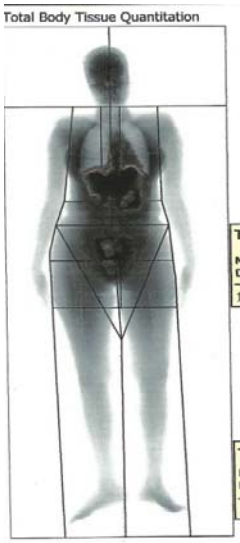
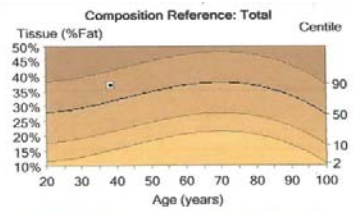
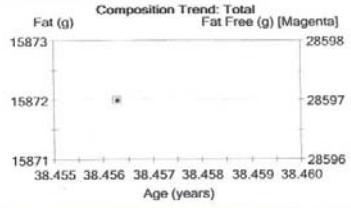


Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score
Neck			
Left	0.882	-1.1	-0.6
Right	0.818	-1.6	-1.0
Mean	0.850	-1.4	-0.8
Difference	0.064	0.5	0.5
Total			
Left	0.840	-1.3	-0.9
Right	0.818	-1.5	-1.1
Mean	0.829	-1.4	-1.0
Difference	0.022	0.2	0.2

FAT CONTENT AND BODY MASS INDEX







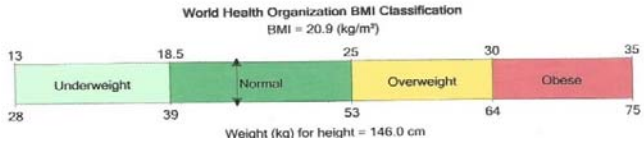
Trend: Total

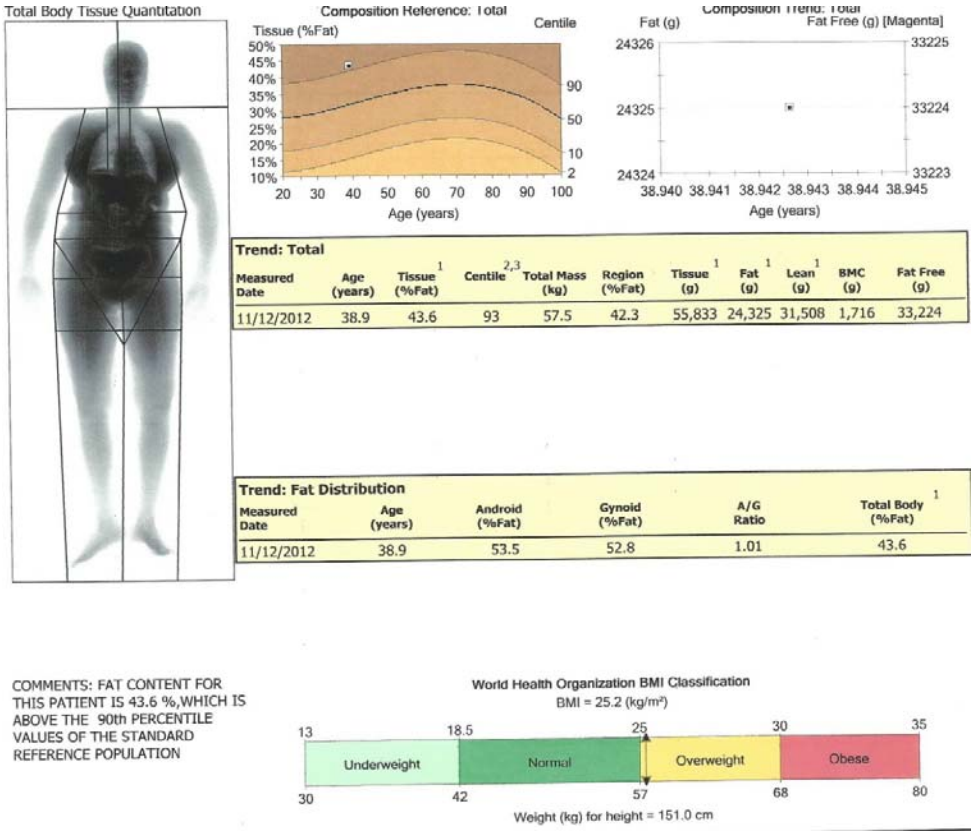
Measured Date	Age (years)	Tissue[1] (%Fat)	Centile[2,3]	Total Mass (kg)	Region (%Fat)	Tissue[1] (g)	Fat[1] (g)	Lean[1] (g)	BMC (g)	Fat Free (g)
16/06/2012	38.4	37.0	75	44.5	35.7	42,875	15,872	27,003	1,594	28,597

Trend: Fat Distribution

Measured Date	Age (years)	Android (%Fat)	Gynoid (%Fat)	A/G Ratio	Total Body[1] (%Fat)
16/06/2012	38.4	40.0	49.9	0.80	37.0

COMMENTS: FAT CONTENT FOR THIS PATIENT IS 37.0 %,WHICH IS BETWEEN THE 50th AND 90th PERCENTILE VALUES OF THE STANDARD REFERENCE POPULATION





All hyperthyroid cases received antithyroid medications for a mean duration of 3.25+/-1.15 months and became clinically & biochemically euthyroid preoperatively. Total thyroidectomy was performed in all subjects. Mean preoperative calcium was in the normocalcemic range in both groups. None of the patients had symptoms of hypocalcemia preoperatively. Postoperatively biochemical hypocalcemia occurred in 40 of 71 subjects i.e. 56.3% (Male: Female= 17:23) including 33 of 40 hyperthyroid cases (Male: Female= 16:17) and 7 of 31 euthyroid controls (M:F=1:6). Thus, the incidence of postoperative hypocalcemia was higher among hyperthyroid cases at 82.5% as compared to 22.5% amongst euthyroid controls. This difference was statistically very significant with

Odd's ratio=16.16, confidence interval 5.005 TO 52.19 and $p<0.001$. Nine of these patients were asymptomatic, 5 among hyperthyroid cases and 4 in euthyoid controls.

Postoperative hypocalcemia with concomitant hypomagnesemia and fall in serum phosphorus was documented in 13 thyrotoxic cases (13 of 40 (i.e.) 32.5%, Male:Female= 7:6). All of these 13 hyperthyroid cases had profound, prolonged hypocalcemia manifesting 72 hours after surgery with cramps, carpopedal spasm and acral parasthesia requiring iv calcium infusion at 1.5-2mg/kg/hr. Oral calcium with vitamin D supplementation was also started simultaneously to high as 3g of calcium carbonate and 1 mcg of alfacalcidol. In addition i.v magnesium sulphate (10mmol/hr) infusion was given in 6 of these patients along with Oral magnesium supplementation. None of our patients had stridor nor cardiac arrhythmia. Three of these patients required calcium supplements for as long as 11 months. However, postoperative hypocalcemia with concomitant fall in phosphorus and magnesium was documented only in 8 patients.

The differences in the biochemical indices and BMD between those hyperthyroid hypocalcemic patients who developed Hungry bone syndrome and those who did not develop HBS are given in the table.

HBS VS NON HBS HYPOCALCEMIC THYROTOXIC PATIENTS

	HBS VS NON HBS	N	Mean	Std. Deviation	P value
PREOP SERUM CALCIUM	HBS	13	9.2154	.63750	0.638
	NON-HBS	20	9.3200	.60489	
POSTOP SERUM CALCIUM	HBS	13	7.6077	.73650	0.425
	NON-HBS	20	7.4050	.68324	
FOLLOW UP SERUM CALCIUM	HBS	13	9.0769	.66728	0.150
	NON-HBS	20	8.6900	.77589	
PREOP SERUM PHOSPHORUS	HBS	13	4.2308	.89479	0.79
	NON-HBS	20	4.1570	.70392	
POSTOP SERUM PHOSPHORUS	HBS	13	3.2854	1.04161	0.001
	NON-HBS	20	4.7150	1.10752	
FOLLOW UP PHOSPHORUS	HBS	13	3.6769	.63921	0.151
	NON-HBS	20	4.0045	.61540	
PREOP SERUM MAGNESIUM	HBS	13	1.5762	.63117	0.060
	NON-HBS	20	2.0205	.64288	
POSTOP SERUM MAGNESIUM	HBS	13	1.4646	1.05822	0.009
	NON-HBS	20	2.1980	.42276	
FOLLOW UP SERUM MAGNESIUM	HBS	13	2.0431	.29775	0.000
	NON-HBS	20	2.4050	.22118	
PREOP INTACT PARATHORMONE	HBS	13	55.0846	48.70439	0.372
	NON-HBS	20	43.0400	27.77997	
POSTOP INTACT PARATHORMONE	HBS	13	35.0769	26.74983	0.168
	NON-HBS	20	23.4400	20.55014	
FOLLOW UP INTACT PARATHORMONE	HBS	13	72.1692	54.86973	0.246
	NON-HBS	20	54.8900	29.11447	
PREOP SERUM ALKALINE PHOSPHATASE	HBS	13	158.6154	66.54264	0.469
	NON-HBS	20	138.6000	82.29881	
POSTOP SERUM ALKALINE PHOSPHATASE	HBS	13	139.6923	42.64658	0.150
	NON-HBS	20	110.8500	61.26068	
FOLLOWUP SERUM ALKALINE PHOSPHATASE	HBS	13	108.0000	53.70289	0.699
	NON-HBS	20	100.3500	55.97394	
SERUM 25 HYDROXYVITAMIN D	HBS	13	23.5577	12.57019	0.625
	NON-HBS	20	25.4840	9.78697	

	HBS VS NON HBS	N	Mean	Std. Deviation	Std. Error Mean	

	HBS VS NON HBS	N	Mean	Std. Deviation	Std. Error Mean	
AGE OF THE PATIENT	HBS	13	39.92	11.332	3.143	0.055
	NON-HBS	20	33.20	8.056	1.801	
GENDER	HBS	13	1.46	.519	.144	0.632
	NON-HBS	20	1.55	.510	.114	
PREOP BMD FEMUR	HBS	13	.77715	.138878	.038518	0.073
	NON-HBS	20	.88110	.168203	.037611	
POSTOP BMD FEMUR	HBS	13	.84785	.141884	.039352	0.075
	NON-HBS	20	.95190	.168256	.037623	
PREOP BMD LUMBAR	HBS	13	.87523	.137741	.038203	0.007
	NON-HBS	20	1.02445	.149185	.033359	
POSTOP BMD LUMBAR	HBS	13	.97208	.156032	.043275	0.039
	NON-HBS	20	1.09635	.165721	.037056	
PREOP BMD FOREARM	HBS	13	.64469	.115370	.031998	0.874
	NON-HBS	20	.63800	.118045	.026396	
POSTOP BMD FOREARM	HBS	13	.63769	.087439	.024251	0.523
	NON-HBS	20	.66175	.114147	.025524	
PREOP FEMUR T SCORE	HBS	13	-2.23846	.901423	.250010	0.047
	NON-HBS	20	-1.44500	1.173154	.262325	
POSTOP FEMUR T SCORE	HBS	13	-1.53077	.786749	.218205	0.045
	NON-HBS	20	-.61000	1.454901	.325326	
PREOP LUMBAR T SCORE	HBS	13	-2.7538	1.21011	.33562	0.015
	NON-HBS	20	-1.6600	1.18117	.26412	
POSTOP LUMBAR T SCORE	HBS	13	-1.9769	1.38633	.38450	0.041
	NON-HBS	20	-.9650	1.29301	.28913	
PREOP FEMUR Z SCORE	HBS	13	-1.2385	1.11096	.30812	0.227
	NON-HBS	20	-.7150	1.24024	.27733	
POSTOP FEMUR Z SCORE	HBS	13	-.7846	1.06759	.29610	0.132
	NON-HBS	20	-.1800	1.11572	.24948	
PREOP LUMBAR Z SCORE	HBS	13	-1.86923	1.095738	.303903	0.010
	NON-HBS	20	-.79000	1.111613	.248564	
POSTOP LUMBAR Z SCORE	HBS	13	-1.2769	1.22757	.34047	0.033
	NON-HBS	20	-.3650	1.09317	.24444	

The mean postoperative serum phosphorus and magnesium was significantly lower in the HBS subgroup as compared to non-HBS subgroup. Further, BMD was significantly lower at femur and lumbar vertebrae among those who developed hungry bone syndrome. In addition, postoperative PTH was normal or high normal in 10 of 13 patients with HBS. Therefore hypoparathyroidism is unlikely to be the cause of hypocalcemia among HBS subgroup.

	HBS	**HYPOCALCEMIA**	
	cases	**cases**	**Control**
Normal PTH	7	21	2(28.57%)
Low PTH	3	6	5(71.4%)
High PTH	3	4	-
Total	13	33	7

On the other hand, among euthyroid controls, transient hypoparathyroidism occurred in 5 of 7 patients with hypocalcemia (71.4%) and was the major determinant of postoperative hypocalcemia. 2 patients had severe hypocalcemia requiring i.v calcium gluconate and oral supplementation. Hypocalcemia and hypomagnesemia were

observed in 3 of these patients requiring oral calcium and magnesium supplementation. In another three patients, in the absence of biochemical hypocalcemia, symptoms of neuromuscular irritability occurred and were found to have hypomagnesemia. Mean preoperative & postoperative S.Magnesium were 2.17+/-0.454 and 1.95+/-0.46 mg/dl respectively among controls. Thus, there was significant fall in serum magnesium level in the postoperative period (p0.039) among controls in our series.

	Cases	**Control**
Mild hypocalcemia	11	5
Moderate hypocalcemia	5	2
Severe Hypocalcemia	15	-
Mild hypomagnesemia	6	-
Severe Hypomagnesemia	13	3
Hypomagnesemic hypocalcemia	9	3

Interestingly, preoperative serum magnesium were found to be lower in patients with Hypomagnesemic hypocalcemia syndrome in both study and control group.

Among hyperthyroid patients, the higher the T3 concentration during hyperthyroidism and longer the duration of hyperthyroidism, the

greater was the subsequent increase in lumbar and femoral BMD. However, this was not statistically significant. Further, BMD did not have correlation with advancing age nor hypovitaminosis. There was strong correlation between BMD and serum alkaline phosphatase($p<0.05$).

Hypovitaminosis D was prevalent in either group. The mean serum 25 OH Vitamin D was 24.27+/-10.61 ng/ml among hyperthyroid vs. 26.12+/-14.63 ng/ml among controls ($p= 0.804$).

DISCUSSION

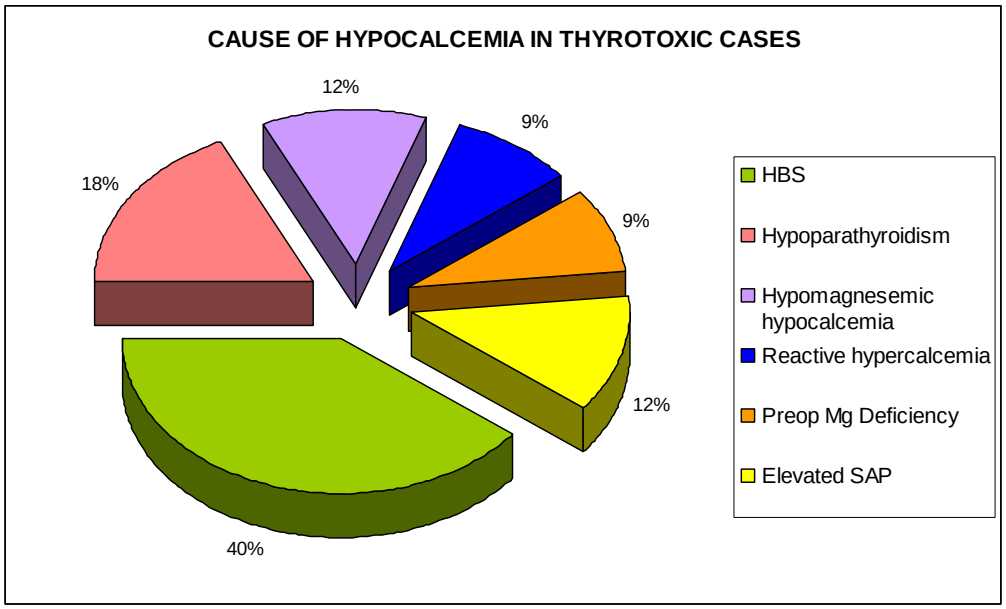
Postoperative hypocalcemia is a common complication after total thyroidectomy with a reported incidence varying from 1.6 to above 50% and the cause is multifactorial. Hypoparathyroidism, being the most widely accepted cause. Hungry bone syndrome characterized by rapid, profound and prolonged hypocalcemia associated with hypomagnesemia and hypophosphatemia is well established cause of hypocalcemia after parathyroidectomy for severe hyperparathyroidism. Though HBS is reported to occur post- thyroidectomy in thyrotoxic patients due to reversal of thyrotoxic osteodystrophy, its mechanism of cause is not well studied in prospective trials.

In our study, incidence of postoperative hypocalcemia was 56.38% (40/71), being significantly higher at 82.5% among hyperthyroid /thyrotoxic cases as compared to 22.5% among euthyroid controls ($p<0.001$).

Pretreatment DEXA scan revealed bone involvement (thyrotoxic osteodystrophy) in 85% of thyrotoxic patients as osteopenia in 17 patients (42.5%) and osteoporosis in 19 patients(45%). Baseline BMD was reduced in all three sites at femur, tibia and forearm with simultaneous

elevation of serum alkaline phosphatase indicative of high turnover bone disease.

Out of 40 thyrotoxic cases, biochemical hypocalcemia occurred in 33 cases. Among these hypocalcemic thyrotoxic cases, 13 patients had prolonged hypocalcemia after fourth postoperative day with concomitant hypomagnesemia and fall in serum phosphorus. In all of these patients, pretreatment DEXA revealed thyrotoxic osteodystrophy and 2-3 fold elevation of serum alkaline phosphatase. Amongst these 13 patients, postoperative intact Parathormone were normal in 7 cases(53.8%), high in three case(23.07%) and low in three cases(23.07%). Therefore, hypoparathyroidism cannot be held as a reason for postoperative hypocalcemia in these thyrotoxic cases. Furthermore, concomitant 2-3 fold elevation of serum alkaline phosphatase postoperatively is suggestive of active bone remineralisation. All these factors are suggestive of shift of the calcium ions along with magnesium and phosphorus ions into the hungry bones. Thus, hungry bone syndrome constitutes one of the most important cause of postoperative hypocalcemia after total thyroidectomy in these patients with thyrotoxicosis. The incidence of HBS in the study group was 32.5% (13/40) and constituited 39.5% of the cases of hypocalcemia in the thyrotoxic group.



The occurrence of hungry bone syndrome has been questioned in the literature because these thyrotoxic patients are rendered euthyroid before treatment thereby reversing the osteodystrophy. But treatment with antithyroid drugs are required for more than 6 months for reversal of osteodystrophy. On the other hand, mean duration of preparation with antithyroid drugs in our series was only3.25+/-1.15 months. Posttreatment DEXA revealed osteodystrophy in many as 22.5% of these thyrotoxic patients with elevation of alkaline phosphatase , which was suggestive of ongoing bone remineralisation even 6 months after surgery. Mitchie et al.[8] refutes calcitonin release during surgical manipulation as a cause of hypocalcemia.

Hypomagnesemic hypocalcemia occurred in 4 of the 20 non-HBS hypocalcemic patients in study group (12.12%). Six cases had

hypoparathyroidism (16.12%). Hypomagnesemic hypocalcemia syndrome occurred in 4 cases(12.12%). Reactive hypercalcemia due secondary hyperparathyroidism contributed to 9.09%(3 cases). Three of the thyrotoxic cases had preoperative magnesium deficiency with normal serum alkaline phosphatase (9.09%). In the remaining 4 cases, we documented elevation of alkaline phosphatase(12.12%). In our series, serum alkaline phosphatase had a strong correlation with both pretreatment bone mineral density & postoperative hypocalcemia in the study group ($p<0.05$).

The incidence of postoperative hypocalcemia in euthyroid controls was 22.58%. Hypoparathyroidism was the major determinant accounting 5 of 7 cases(71.4%). However, hypomagnesemia occurred in 7 of the euthyroid controls all of whom were young females. Three of these patients had concurrent hypocalcemia and required magnesium supplementation for resolution of the persistent symptoms despite calcium and vitamin D supplementation. Three other patients had symptoms of neuromuscular irritability in the absence of biochemical hypocalcemia. One other patient was asymptomatic. Thus, 6 of 7 patients (85.7%) with hypomagnesemia were symptomatic. Hypomagnesemic hypocalcemic syndrome (3/7) accounted for 42.8% as a cause of hypocalcemia among euthyroid controls.

Demeester-Mirkine et al.[29] concluded that postthyroidectomy hypocalcemia was multifactorial, due to a combination of hemodilution, temporary parathyroid insufficiency, and in thyrotoxic patients “hungry bone syndrome.”

Wison et al.[6] and Szubin et al. [14] reported that hypomagnesemia may lead to post-thyroidectomy tetany especially in the presence of hypocalcemia.

In our study, actively hyperthyroid patients had significant reduced bone mineral density at femur, lumbar vertebrae and forearm. After six months of definitive surgical management, there was recovery of loss of bone mass at all three sites, but predominantly in the femur and lumbar vertebrae.

The first case of thyrotoxic osteodystrophy was reported in 1891 by Von Recklinghausen[31]. Several radial and longitudinal studies of subjects with hyperthyroidism have demonstrated reduced bone density at various skeletal sites and reversal of bone loss with antithyroid therapy[34, 36-40]. In a prospective study of 50 hyperthyroid patients previously conducted in our department, Udayakumar[43] and co workers have demonstrated 4% increment in lumbar bone mass after one year of surgical management. But BMD was measured only at spine.

The present study demonstrated increase in bone mineral density by 7.58% at femur and 8.27% at lumbar vertebrae after treatment. Although there was increase in BMD in forearm by 2.95%, this improvement in BMD was not statistically significant ($p = 0.081$). A recently published study on 30 hyperthyroid patients of Indian origin, Dhanwal et al[45]., reported similar increase in bone mineral content by 7.4% and 9.3% at hip and spine respectively, but there was deterioration at forearm by 6.7%. Lack of recovery or delayed recovery at forearm may be attributed to the predominance of cortical bone at this site. Cortical bone has lower activation frequency and lesser bone surface for remodeling when compared to trabecular bone. Lumbar vertebra is predominantly composed of trabecular bone. Femur is a composite of trabecular and cortical bone. This explains predominant bone remineralisation at these sites.

As per the literature[41,42], patients with hypovitaminosis D & secondary hyperthyroidism showed significant bone loss at lumbar spine and hip. Mezquita et al[11] & Collins et al[39] reported that BMD at lumbar spine correlated with 25 OH vitamin D3 levels. However, in our present study, the mean Serum 25 OH vitamin D3 was in insufficient range in both study & control group and neither group showed significant change from baseline after definitive treatment. Serum 25 OH vitamin D3 did not

correlate with the bone mineral density and all the 3 control patients with Vitamin D deficiency had normal iDEXA scan. Studies[44,45,46] on Indian population reports similar results.

The mean serum calcium of 9.130+/-0.663 was in the normocalcemic range in contrary to hypercalcemia[32, 33] in western population with hyperthyroidism. The widely prevalent vitamin D deficiency in our population may account for this normocalcemia[46] and consequent secondary hyperparathyroidism. Neither advanced age nor hypovitaminosis D was a significant predictor of reduced bone density in our hyperthyroid patients.

There were a few limitations in our study. We followed our patients for a shorter duration of 6 months only. Bone remineralisation at forearm needs to be studied prospectively for a longer duration of more than a year.

We conclude that Hungry bone syndrome is the major determinant of postoperative hypocalcemia in thyrotoxic patients. Reduced BMD in the femur and lumbar vertebrae with elevated alkaline phosphatase and intact parathormone are important predictive risk factors for postoperative hypocalcemia in thyrotoxic patients.

Transient hypoparathyroidism is the major determinant of postoperative hypocalcemia in euthyoid controls. Magnesium deficiency,

especially in young females are the predictive risk factors for postoperative hypocalcemia in euthyroid patients after total thyroidectomy.

Hence, we recommend routine monitoring of calcium postoperatively in all patients, serum alkaline phosphatase in thyrotoxic patients and magnesium in euthyroid patients especially in young females and those with persistent hypocalcemic symptoms.

CONCLUSION

The incidence of post-thyroidectomy hypocalcemia was significantly higher in thyrotoxic patients than euthyroid controls.

The incidence of hungry bone syndrome was 32.5% and constituted the major determinant of postoperative hypocalcemia among thyrotoxic patients.

Reduced BMD in the femur and lumbar vertebrae with elevated alkaline phosphatase and intact parathormone are important predictive risk factors for postoperative hypocalcemia in thyrotoxic patients.

Transient hypoparathyroidism is the major determinant of postoperative hypocalcemia in euthyoid controls. Magnesium deficiency, especially in young females are the predictive risk factors for post-thyroidectomy hypocalcemia in euthyroid patients.

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PATIENT INFORMATION SHEET

Thyroid is an endocrine gland situated in the front of neck. Thyroid gland synthesizes a chemical substance known as hormone – thyroxine , which is directly released in to the blood stream and has its action on target organs. Some of the thyroid related diseases requires surgery. Thyroidectomy – complete removal thyroid gland. Thyrotoxicosis is a hypermetabolic state due to excess circulating thyroid hormones and affects many organ system.

It may affect the skeletal system and lead to loss of bone mass, which may lead to bone pain, fractures etc. Definitive surgical management reverse the bone loss. These changes in bone mineral density(BMD) can be measured by DEXA scanners. Further there are changes in the level of certain mineral ions such as calcium, phosphorus, magnesium etc. after thyroid surgery. This may cause symptoms of neuromuscular irritability.

In this study we measure changes in the BMD and serum ca, phosphorus etc. before and after surgery. During this study, analysis of results, and publication of the study, the patients identity will not be revealed. The outcome of the study will be revealed to the patient on completion of the study ion request.

Signature of the investigator Signature of the patient

Date

Place

CONSENT FORM

I Ms/Mr._____M/O//F/O, B/O _____

Sex_____Hosp. No._____ admitted in the Department of Endocrine Surgery, Madras Medical College ,Chennai-3 on _____ was explained by the doctor that I am provisionally diagnosed to have a thyrotoxicosis/ multinodular Goitre .

This condition requires thyroidectomy after work up and confirmatory diagnosis.

I am willing to be enrolled in the study undertaken to evaluate hungry bone syndrome in thyrotoxicosis as a cause of postoperative hypocalcemia with the aid of blood investigations, TFT, FNAC (invasive procedure) and DEXA (non invasive). The doctors have explained to me the nature and the purpose of the study.

I have given my consent only after completely understanding the details that were explained to me.

I am willing to be enrolled in this study without any compulsion.

I a am fully aware that I can withdraw from the trial at any time during the study and even then routine treatment as per the hospital protocol for the thyroid disease will be continued.

I am willing to go through DEXA scanner, a machine that produces two X-ray beams, each with different energy levels. One beam is high energy while the other is low energy. The amount of X-rays that pass through the bone is measured for each beam. This will vary depending on the thickness of the bone. Based on the difference between the two beams, the bone density can be measured. The radiation exposure from a DEXA scan is actually much less than that from a traditional chest X-ray.

The precautions and adverse effects of DEXA used for analysing Bone mineral density were explained to me

I have also given my consent for drawing blood sample for biochemical analysis during the study.

I have given this consent to be enrolled in this study with my full consciousness

Signature of the Investigator Signature of Patient

Date : 11/11/2011
Place: Chennai -3.

PROFORMA

DATE

NAME

AGE

SEX

I.P.NUMBER

DIAGNOSIS

THYROID FUNCTION TEST

FREE TRIIODOTHYRONINE

FREE TETRAIODOTHYRONINE

THYROID STIMULATING HORMONE

ULTRASOUND OF THE THYROID

Sl.no	Parameters	Study group			Control Group		
		Pre treatment	Post op	Follow up	Pre treatment	Post op	Follow up
1	Bone Mineral Density-DEXA						
2	S. Corrected Calcium						
3	S. Phosphorus						
4	S. Magnesium						
5	S. Parathormone						
6	S. Alkaline Phosphatase						
7	S. 25–OH Vitamin D						

SL. NO	NAME	AGE	SEX	GROUP	P Ca	PO Ca	F Ca	P Ph	PO Ph	F Ph	P Mg	PO Mg	F Mg	P PTH	PO PTH	F PTH	P SAP	PO SAP	F SAP	P VITD	Tross	iv cal	PREOP BMD FEMOR	POSTOP BMD FEMUR	PREOP BMD LUMBAR	POSTOP BMD LUMBAR	PREOP BMD FOREARM	POSTOP BMD FOREARM
1	KASTHURI	55	F	CASE	8.3	8.7	8.7	3.9	5.8	4.6	0.86	1.72	2.2	77.5	35	75	131	118	145	24	1	1	1.086	1.084	1.231	1.232	0.626	0.651
2	NATARAJAN	61	M	CASE	8	8.3	9.2	2.2	1.7	2.7	0.96	0.8	1.72	54.5	36.1	80.4	87	173	112	55	2		0.618	0.648	0.724	0.79	0.544	0.561
3	HABIBULLAH	34	M	CASE	8.6	8.6	9	4.2	4.6	2.8	1.13	2	1.9	35.5	45.6	44.9	103	122	64	34	2	1	1.126	1.119	1.28	1.394	0.663	0.739
4	MANOHARI	32	F	CASE	9.2	7.2	9.3	4.4	7.1	5	0.7	2.4	2.4	21.4	5.49	9	79	63	77	23	3	3	0.934	1.144	0.838	1.088	0.605	0.601
5	PADMAVATHY	35	F	CASE	9.3	8	9.1	4.6	4.5	4.4	0.91	1.04	1.8	49.4	0.4	42	137	113	86	22.1	2	2	1.104	1.106	1.112	1.152	0.654	0.658
6	DEVI	27	F	CASE	9.3	8.6	10	4.6	2.6	4	0.9	1.04	1.64	81.3	68.9	177	166	141	73	10	2	1	0.853	0.941	1.101	1.276	0.884	0.843
7	VIJAYKUMAR	47	M	CASE	8.9	8.3	9.4	4	2.4	3.1	0.88	0.97	1.8	26.1	47.3	33	137	179	66	35	2	1	0.84	0.924	0.926	1.124	0.736	0.743
8	VALLI	27	F	CASE	9.4	8.2	9.2	4.5	3.4	3.5	0.85	2.3	2.4	43.3	16.3	37.3	40	41	41	14	2	2	1.13	1.161	1.036	1.046	0.717	0.666
9	LAKSHMIKANTHA	40	F	CASE	8.8	8.9	9.3	3.8	3.7	2.5	1.5	3	2.3	79.3	29.9	28.8	74	77	61	22	1	1	0.904	0.944	1.201	1.242	0.648	0.689
10	MEGALAGANDHI	22	F	CASE	10.5	8.2	9.1	3.7	3.9	3.4	0.95	1.4	2.7	71.1	25.8	67.3	70	65	55	34	1	1	0.903	1.034	1.146	1.256	0.652	0.626
11	RAVI	33	M	CASE	9.1	8.6	9.4	4.6	3.9	3.5	0.8	0.83	1.7	20.7	29.7	23	140	118	86	21	2	2	0.87	0.923	0.96	1.121	0.83	0.887
12	ANJALI	25	F	CASE	9.7	7.8	9.4	4.9	4.9	4	1.39	0.99	1.8	60.4	44.2	48	169	111	78	24	2	2	0.809	0.886	0.789	0.876	0.557	0.608
13	ELANJIUM	34	F	CASE	10	7.2	8.8	4.3	3.2	3.8	1.9	1.2	2.2	37.5	68.5	68.5	135	119	115	11.29	3	2	0.867	0.951	0.986	1.046	0.786	0.687
14	VEERABATHIRAN	42	M	CASE	8.7	5.9	8.1	2.6	3.6	5.5	2.6	1.33	2.4	64.6	0.01	16	82	61	74	21.3	3	3	1.233	1.241	1.425	1.529	1.038	1.032
15	INDIRA	30	F	CASE	9.8	7.8	8	4.6	4.7	3.44	2.5	1.7	2.7	16.9	60	60	119	84	78	20.4	2	2	0.79	0.894	1.089	1.168	0.558	0.594
16	SUSHEELA	27	F	CASE	9	7.9	8.4	3.6	4	3.4	1.3	1.5	1.9	27.3	18.9	28	103	76	77	14.24	2	1	0.823	0.926	0.907	1.046	0.679	0.688
17	NABEESA BEGAM	25	F	CASE	8.2	9.4	9.4	2.4	3.2	3	1.5	1.5	1.2	72.8	24.1	62.6	73	73	74	6.91	1	1	0.889	0.882	1.119	1.134	0.776	0.685
18	ABIRAMI	35	F	CASE	10.5	8.5	8.1	5.8	3.4	3.2	2.41	1.2	2.3	9.6	82.1	80	89	97	85	22.1	3	2	0.733	0.829	0.871	0.938	0.751	0.632
19	JAYANTHI	44	F	CASE	9.4	6.6	7	5.3	6.2	4.2	1.7	1.53	2.5	61	8.6	72	81	81	50	33.6	3	3	0.841	0.973	1.039	1.065	0.635	0.82
20	ELUMALAI	50	M	CASE	8.8	6.5	9.2	4.1	1.41	2.8	1.04	4.9	2.2	92.1	0.1	62	197	129	78	34	3	3	0.812	0.924	0.948	1.046	0.565	0.599
21	SELVAM	57	M	CASE	9.3	7.2	8	4.5	3.8	4.6	1.8	1.2	2.7	5	19	193	148	176	248	10	2	1	0.691	0.827	0.806	0.907	0.608	0.603
22	DURGADEVI	26	F	CASE	9.2	7.5	8.2	3.8	5.5	4.4	2.2	2.2	2.4	58.7	16.6	121.6	137	117	144	18	3	3	0.86	0.991	1.065	1.111	0.62	0.615
23	ELUMALAI.B II	40	M	CASE	9.4	7	9.8	5.2	4.2	4.6	2.5	2.2	2.2	5.7	41	83.6	140	212	196	23.9	1	1	0.732	0.765	0.798	0.853	0.58	0.605
24	VALLI II	28	F	CASE	9.4	7	8.1	3.7	4.8	4.25	2.4	2.4	2.5	11.9	0.1	61.9	84	116	100	11.8	3	3	0.872	0.909	1.058	1.131	0.608	0.614
25	RADHA/MUNIYAMMAL	48	F	CASE	9	8	9.3	5.1	4.8	4.2	2.4	2.9	2.8	35.1	16	42.4	87	67	59	34.61	2	1	0.616	0.615	0.727	0.701	0.454	0.468
26	SHANAVAS	45	F	CASE	8	8.4	9	4.3	4.6	4.2	2.4	2.9	2.4	74.8	46.6	67.7	157	104	84	12.98	1	1	0.855	0.863	0.951	0.983	0.551	0.608
27	DHANALAKSHMI	47	F	CASE	8	6.9	9	3.24	5.3	4.8	2.4	3	2.7	26.2	13.3	33	154	113	82	27.83	3	3	0.904	0.946	1.001	1.038	0.652	0.704
28	MATHIAZHAGI	22	F	CASE	10.5	7.6	9.6	5	4.1	4.2	2.3	2.3	2.4	2	47.1	48	331	194	101	45.46	2	1	0.97	1.062	1.088	1.172	0.618	0.643
29	DEVAKURUBAI	27	F	CASE	9.9	6.9	8.6	4.9	3.6	3.8	2.2	2.3	2.2	17	6	33	235	206	102	17.32	3	3	0.718	0.809	0.966	1.124	0.513	0.598
30	VELU	32	M	CASE	9.1	7	9.1	3.6	4.6	3.4	2.3	2.2	2.3	68.7	30.6	84.9	109	94	78	24.35	3	2	0.873	0.924	1.163	1.194	0.663	0.726
31	RAVI II	44	M	CASE	8	8.4	8.6	3.5	3.8	3.6	2.3	2.4	2.2	84.7	50.9	68.7	215	155	176	34.09	1	1	0.595	0.628	0.776	0.854	0.524	0.576
32	SHERIFF	40	M	CASE	9	7.2	6.8	4.8	4	2.9	2.3	2.3	2.2	51.1	17.3	87.7	185	96	278	24.07	2	1	0.637	0.688	0.883	0.9	0.489	0.553
33	RAJA	30	M	CASE	8.7	8.3	9.1	4.7	4.9	3.4	2.3	2.2	2.3	14	57.5	73.7	226	151	151	48.8	2	2	0.82	0.889	0.909	0.957	0.592	0.623
34	SIVAKUMAR	27	M	CASE	9.5	6.4	9.2	4.2	4.7	4.1	2.7	2.3	2.2	55	12.8	62	260	207	106	20.9	2	1	0.722	0.834	0.944	1.132	0.59	0.622
35	BALASUBRAMANIAM	40	M	CASE	10	8.2	9.4	3.7	4.2	3.9	0.81	2.3	1.9	32.5	71.2	97	117	78	116	15	2	2	0.664	0.71	1.042	1.207	0.664	0.618
36	singaravelu	40	M	CASE	8.9	7.2	8.6	3.6	3.8	4	2.3	2.3	2.6	121.3	33.2	29.8	253	251	182	28.8	2	2	0.965	0.989	0.848	0.876	0.671	0.675
37	SIVAKUMAR3	31	M	CASE	9	8.1	8.8	3.7	7.3	3.8	2.3	2.3	2.2	38.9	20.9	36.9	81	110	97	24.5	2	2	1.027	1.029	1.068	1.081	0.71	0.725
38	KANIAPPAN	29	M	CASE	9.2	7.9	9.3	4	3.8	3.9	2.2	2.3	2.3	50.1	10	24.3	42	22	36	21.94	3	3	1.143	1.196	1.154	1.151	0.711	0.712
39	SARAVANAN	38	M	CASE	8.5	8.1	10	3.5	3.4	3.8	2.2	1.7	2.1	184	20.8	24.3	342	97	88	27.55	2	1	0.539	0.582	0.69	0.772	0.515	0.529
40	SHANMUGAM	43	M	CASE	9.1	6.1	8.6	3.7	3.2	3.4	2.3	1.3	2.2	83.2	8.7	18.4	212	193	102	17.07	3	3	0.682	0.713	0.72	0.811	0.522	0.534

SL. NO	NAME	AGE	SEX	GROUP	P Ca	PO Ca	F Ca	P Ph	PO Ph	F Ph	P Mg	PO Mg	F Mg	P PTH	PO PTH	F PTH	P SAP	PO SAP	F SAP	P VITD	Tross	iv cal	PREOP BMD FEMOR	POSTOP BMD FEMUR	PREOP BMD LUMBAR	POSTOP BMD LUMBAR	PREOP BMD FOREARM	POSTOP BMD FOREARM
1	MANJULA	35	F	CONTROL	9.8	8.6	8.8	4	3.9	4.5	3.1	1.4	1.9	36.2	0.01	40.1	51	42	46	18.03	2	1	0.995	0.997	1.223	1.234	0.915	0.901
2	JANSI	34	F	CONTROL	9.6	8.6	8	4.1	4.46	4	3.3	1.8	2.3	48.1	7.4	33.3	88	79	76	12.08	2	2	0.897	0.901	1.014	1.012	0.74	0.758
3	PUSHPALATHA	27	F	CONTROL	9.2	8.2	8.5	4.5	5.4	4.2	1.2	1	2.5	65.6	0.01	65.1	64	57	41	9.2	2	1	1.09	1.11	1.291	1.289	0.89	0.899
4	SELVI	26	F	CONTROL	9.4	9.3	9.1	3.9	3.4	3.4	2.7	0.9	2.4	60.7	32.3	39.4	51	51	59	11.46	1	1	1.045	1.043	1.271	1.269	0.655	0.674
5	ANISHA	25	F	CONTROL	8.8	8.2	8.7	2.4	2.9	1.7	1.58	2.01	2.4	55.8	17.6	55.2	75	63	67	15.66	2	1	1.096	1.098	1.112	1.114	0.843	0.832
6	SELVI VENDA	40	F	CONTROL	8.3	7.6	9.1	3.2	3.8	3.4	1.7	1.83	2.1	23	18.8	48	65	63	71	16.89	2	1	1.082	1.84	1.238	1.2236	0.739	0.734
7	SRIDHAR	37	M	CONTROL	8.3	8.5	9.3	2.4	3.2	3.8	1.56	1.4	1.31	49.9	14.9	42.3	78	77	77	14.2	2	1	0.947	0.976	1.11	1.053	0.737	0.744
8	SRINIVASAN	34	M	CONTROL	10.6	7.6		5.3	4.6		2.2	2.6		77.9	13.5		81	57		20.3	3	1	0.959	0.923	1.098	1.046	0.711	0.734
9	POONGAVANAM	38	F	CONTROL	9.6	8.6	9.1	3.3	4.3	3.8	1.73	1	2.1	36.8	17.8	44	31	34	56	8.61	1	1	0.985	0.984	1.212	1.232	0.838	0.832
10	THILAGAVATHY	30	F	CONTROL	9.6	9.2	6.1	2.1	3.9	5.3	1.85	2.1	1.31	28.5	22	19.9	59	56	61	13.85	1	1	0.872	0.873	0.995	1.004	0.671	0.662
11	AMULRANI	25	F	CONTROL	9.2	9	8	5	6.2	5.2	2	1.37	2	66.9	0.1	7	113	78	74	24.6	2	2	0.966	0.972	1.095	1.1	0.837	0.845
12	SELVARAJ	52	M	CONTROL	10.6	10	9.4	3.1	4.1	4	1.8	2	2.5	26	19.8	59	74	94	40	38	1	1	0.983	0.994	1.146	1.148	0.75	0.746
13	KARPAGAM	26	F	CONTROL	10.4	8.2	9.2	4.4	4.4	4.5	1.6	2.1	2.4	48.6	11.9	56	98	71	79	45	2	1	0.79	0.794	0.928	0.932	0.581	0.605
14	SHANTHI P	45	F	CONTROL	9.1	8.8	9.5	3.6	4.3	4.4	2.4	2.1	2.6	24	5.5	15.6	56	40	43	19.4	1	1	1.082	1.083	1.113	1.109	0.798	0.796
15	NINEYAPAN	45	M	CONTROL	9.9	10.3	9.6	4.3	4.7	4.2	2.3	2	2.2	2	1	22	72	69	76	52.2	2	1	0.949	0.952	1.028	1.42	0.999	0.976
16	AMBIKA	23	F	CONTROL	9.9	9.4	9.2	4.8	5.2	4.4	1.82	1.9	2.4	57.1	30.1	27.8	41	41	67	19.2	1	1	0.991	0.996	1.03	1.04	0.784	0.792
17	DILSHAD	28	F	CONTROL	9.3	8.3	8.9	3.7	4.3	3.1	1.71	2.01	2.7	46	9.9	37.5	49	46	46	44.5	2	2	0.958	0.956	1.027	1.033	0.652	0.655
18	DURAISAMY	46	M	CONTROL	9.5	9.4		3.7	3.5		2.2	1.32		39.1	25.3		58	57		55.48	1	1	0.799	0.799	0.915	0.922	0.647	0.685
19	JAIBUNBEE	40	F	CONTROL	9.7	9.4	9.3	4.8	3.9	4.1	2.4	2.4	2.4	40.3	20.8	33.4	91	80	76	33.7	1	1	1.031	1.033	1.089	1.088	0.735	0.744
20	SUGUNA D	41	F	CONTROL	9.7	9	9.2	4.9	4	3.8	2.5	2.3	2.2	49.3	44.5	48	58	48	56	22.47	1	1	1.046	1.048	1.161	1.152	0.858	0.854
21	DIVYA	23	F	CONTROL	9	8	8.4	4.5	5.4	4.6	2.5	2.5	2.4	58.9	21.3	67.2	68	96	60	14.86	2	2	0.897	0.901	1.092	1.118	0.554	0.609
22	MOORTHI	38	M	CONTROL	10	11	9.1	3.74	3.8	4.5	2.5	2.4	2.6	28.6	17.6	38.5	120	112	80	17.28	1	1	1.083	1.084	1.051	1.062	0.795	0.803
23	LAKSHMI	23	F	CONTROL	10	9	9.4	4.2	4	3.8	2.4	2.4	2.2	48.4	35.8	44	42	35	56	23.5	1	1	0.949	0.953	1.133	1.121	0.574	0.579
24	ADHILAKSHMI	30	F	CONTROL	9	8.7	9.2	3.7	3.9	3.6	2.3	2.2	2.6	45	23	46	57	76	56	17.39	1	1	1.011	1.017	1.125	1.115	0.739	0.741
25	POONGODI	43	F	CONTROL	9	9	8.6	3.8	4.9	3.6	2.2	2.2	2.3	53.1	30	71.4	68	60	57	16.89	1	1	1.135	1.136	1.398	1.389	0.807	0.812
26	JAMMUNA	44	F	CONTROL	10	9.1	9.3	4.6	5.4	2.5	2.3	2.3	2.2	30.3	14.3	29.9	107	89	95	27.42	1	1	1.054	1.064	1.206	1.199	0.677	0.678
27	CHARULATHA	27	F	CONTROL	11	10.2		3.9	3.6		2.3	2.2		61.2	54		125	105		28.37	1	1	1.076	1.084	1.164	1.169	0.691	0.678
28	DHANAM	30	F	CONTROL	7.9	9.9	9.1	5.5	4.6	4.3	2.5	2.3	2.3	25.9	12	30.2	61	54	67	50.95	1	1	1.029	1.033	1.165	1.168	0.722	0.712
29	DEEPA	18	F	CONTROL	9.2	9	8.8	5.3	4.6	4.3	2.5	2.1	2.4	15.6	10	19.6	81	56	77	31.02	2	2	0.949	0.967	1.049	1.053	0.615	0.654
30	RAJENDRAN	50	M	CONTROL	8	9	8.7	3.5	3.5	3.8	2.2	2.3	2.2	35.4	30.9	66.5	84	63	84	61.68	1	1	1.104	1.099	1.141	1.143	0.799	0.789
31	THULUKANAM	28	M	CONTROL	9.5	8.7	8.6	3.7	3	3.4	2.2	2.2	2.6	36.4	23.3	33.5	65	87	74	25.6	2	1	1.528	1.53	1.407	1.411	0.929	0.927

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. K. Poongkodi
PG in MCH Endocrine Surgery
Madras Medical College, Chennai -3

Dear Dr. K. Poongkodi

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Hungry bone syndrome in Thyrotoxicosis as a cause of postoperative hypocalcemia – A prospective study " No. 25112011

The following members of Ethics Committee were present in the meeting held on 22.11.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2.	Prof.A. Sundaram MD Vice principal, Madras Medical College, Ch -3	-- Member Secretary
3.	Prof. R. Nandhini MD Director, Institute of Pharmacology ,MMC, Ch-3	-- Member
4	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
5.	Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. Md Ali MDDM Prof & Head , Dept. of MGE, MMC,Ch-3	-- Member
7. .	Prof. Shantha Ravishankar MD Prof of Neuropathology, MMC, Ch-3	-- Member
8.	Thiru. S. Govindsamy. BA BL	-- Lawyer
9.	Tmt. Arnold soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

पी.ए.बी.एक्स./PABX : 26588980, 26588707, 26589336, 26589745, 26589873, 26589414
फैक्स/FAX : 011-26588662, 011-26589791, 011-26589258

तार / GRAM : विज्ञानी / SCIENTIFIC
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भारतीय आयुर्विज्ञान अनुसंधान परिषद
INDIAN COUNCIL OF MEDICAL RESEARCH

स्वास्थ्य अनुसंधान विभाग (स्वास्थ्य एवं परिवार कल्याण मंत्रालय)
वी. रामलिंगस्वामी भवन, अन्सारी नगर, नई दिल्ली - 110 029

DEPARTMENT OF HEALTH RESEARCH (MINISTRY OF HEALTH & FAMILY WELFARE)
V. RAMALINGASWAMI BHAWAN, ANSARI NAGAR, NEW DELHI - 110 029

No.3/2/2012-13/PG-thesis-HRD-29
Dated: 11.9.12

Sandhya Diwakar
Scientist- E

To,
Dr. K. Poongkodi MS
Department of Endocrine Surgery,
Madras Medical College,
Chennai-600003, poongkodithesurgeon@gmail.com

Dear Dr. K. Poongkodi MS

This is with reference to your application seeking financial assistance from the Council for MD/MS/DM/MCH dissertation thesis entitled "Hungry bone syndrome in thyrotoxicosis as a cause of postoperative hypocalcemia – A prospective study".

I am glad to inform you that Director General, ICMR, based on the recommendation of Expert Committee, has sanctioned a sum of Rs. 25, 000/- (Twenty five thousand only) to you for providing an electronic and hard copy of your dissertation thesis to the Council. Mandatory requirement to avail this opportunity is to provide us with an undertaking duly forwarded through the guide, to the undersigned, enabling us to release the grant.

This is to inform you that Rs. 25,000/- will be disbursed to you in two installments. Initial amount of Rs. 15,000/- after receipt of the undertaking as per the guidelines and remaining amount of Rs. 10,000/- on receipt of the electronic copy, hard copy and summary of work done of your dissertation thesis duly approved by the University/ Institute along with one publication in a reputed Journal.

With best wishes,

Yours Sincerely,

SDiwakar

(Sandhya Diwakar)
011-26589287
sandhyadiwakar@yahoo.com

Copy to: Dr. M. Chandrasekaran, Professor & Head, Department of Endocrine Surgery, Madras Medical College, Chennai-600003

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INDIAN COUNCIL OF MEDICAL RESEARCH

स्वास्थ्य अनुसंधान विभाग (स्वास्थ्य एवं परिवार कल्याण मंत्रालय)
वी. रामलिंगस्वामी भवन, अन्सारी नगर, नई दिल्ली - 110 029

DEPARTMENT OF HEALTH RESEARCH (MINISTRY OF HEALTH & FAMILY WELFARE)
V. RAMALINGASWAMI BHAWAN, ANSARI NAGAR, NEW DELHI - 110 029

No.3/2/2012-13 /PG-Thesis-HRD-29
Dated: 15.10.2012

To

Dr. M. Chandrasekaran,
Professor & Head,
Dept of Endocrine Surgery,
Madras Medical College,
Chennai-600003.

Subject: Payment of Rs.15000/- under MD/MS/DM/MCH Thesis financial assistance programme of ICMR, Human Resource Development entitled, "Hungry bone syndrome in thyrotoxicosis as a cause of postoperative hypocalcemia- A prospcctive study".

Sir,

The Director General sanctions the payment of 1st installment of Rs.15000/-(Rupees fifteen thousand only) as the award under MD/MS/DM/MCH thesis financial assistance programme of ICMR, Human Resource Development.

A bank draft for the amount of Rs.15000/- will be sent to you in due course. The grant has been sanctioned on the conditions laid down in Council's rules.

Second installment will be given after receiving the copy of thesis etc as mentioned in award letter.

Yours faithfully,

(SHASHI ARORA)
Administrative Officer
For Director General

Copy to:

1. Accounts-I, ICMR along with a formal bill of Rs.15000/- (Rupees fifteen thousand only) for payment of 1st installment at an early date from allocation made under the scheme (2012-13), Div of HRD. The expenditure may be met related to "17-P" Human Resource Development Plan.
2. Candidate's Name: Dr. K. Poongkodi MS, Dept of Endocrine Surgery, Madras Medical College, Chennai-600003.
3. Dean, Madras Medical College, Chennai-600003.

Shashi Arora
Administrative Officer
For Director General

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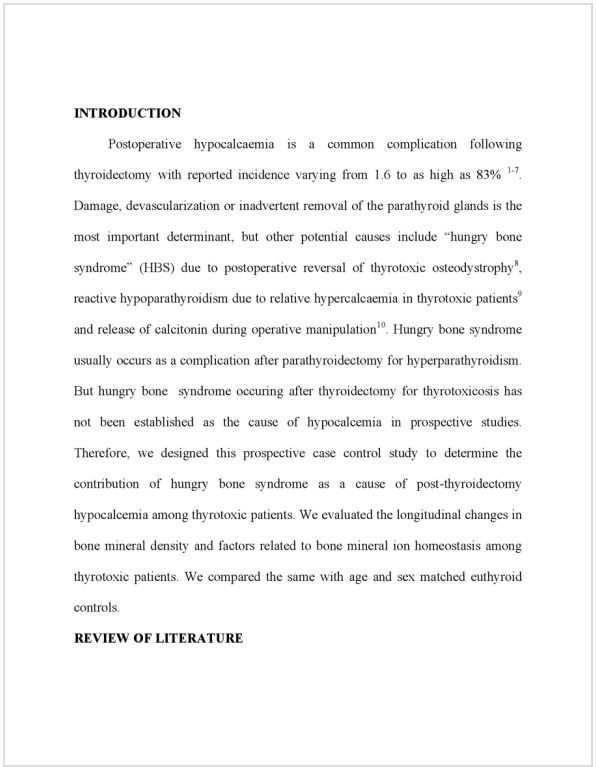

INTRODUCTION

Postoperative hypocalcaemia is a common complication following thyroidectomy with reported incidence varying from 1.6 to as high as 83% [1-7]. Damage, devascularization or inadvertent removal of the parathyroid glands is the most important determinant, but other potential causes include "hungry bone syndrome" (HBS) due to postoperative reversal of thyrotoxic osteodystrophy[8], reactive hypoparathyroidism due to relative hypercalcaemia in thyrotoxic patients[9] and release of calcitonin during operative manipulation[10]. Hungry bone syndrome usually occurs as a complication after parathyroidectomy for hyperparathyroidism. But hungry bone syndrome occuring after thyroidectomy for thyrotoxicosis has not been established as the cause of hypocalcemia in prospective studies. Therefore, we designed this prospective case control study to determine the contribution of hungry bone syndrome as a cause of post-thyroidectomy hypocalcemia among thyrotoxic patients. We evaluated the longitudinal changes in bone mineral density and factors related to bone mineral ion homeostasis among thyrotoxic patients. We compared the same with age and sex matched euthyroid controls.

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